

Figure 1

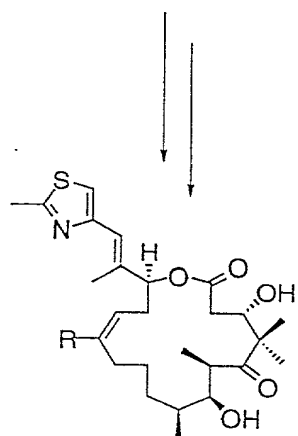
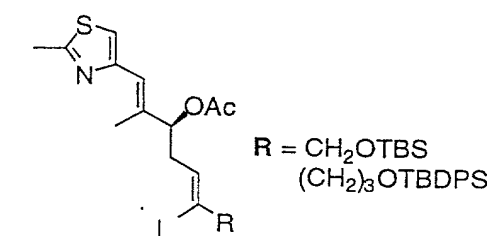
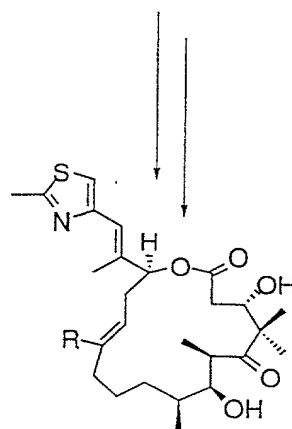
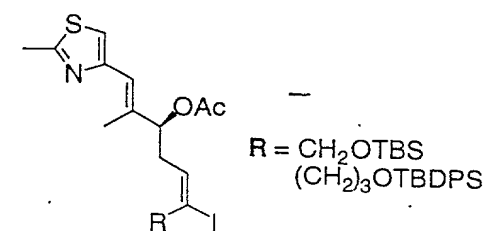
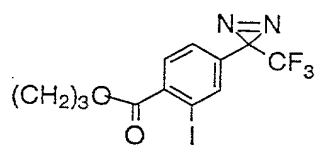
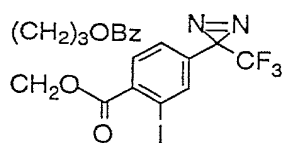

$$R = \text{CH}_2\text{OH}$$
$$(\text{CH}_2)_3\text{OH}$$

$$R = \begin{matrix} \text{CH}_2\text{OH} \\ (\text{CH}_2)_3\text{OH} \end{matrix}$$

Figure 2

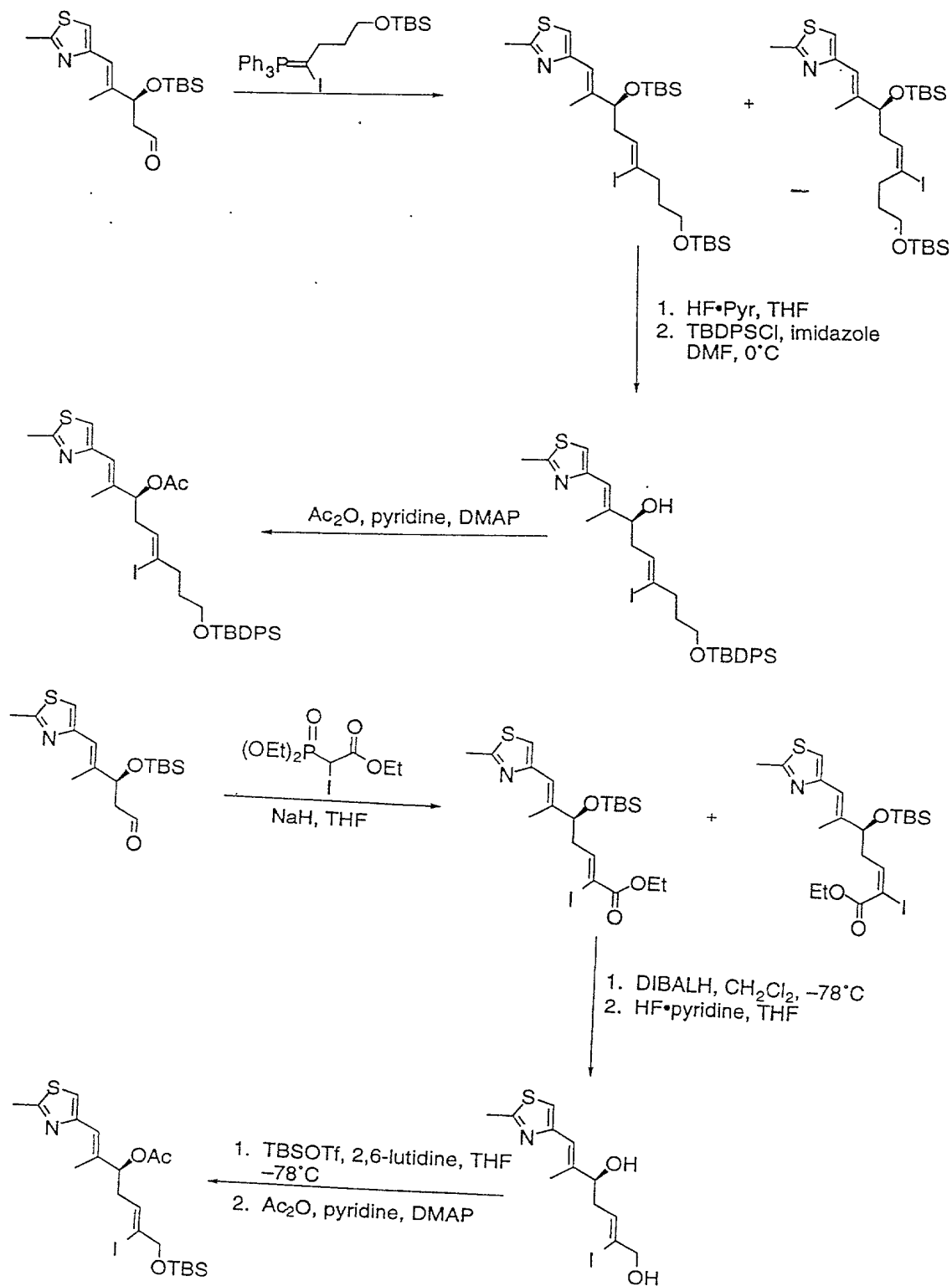


Figure 3(A)

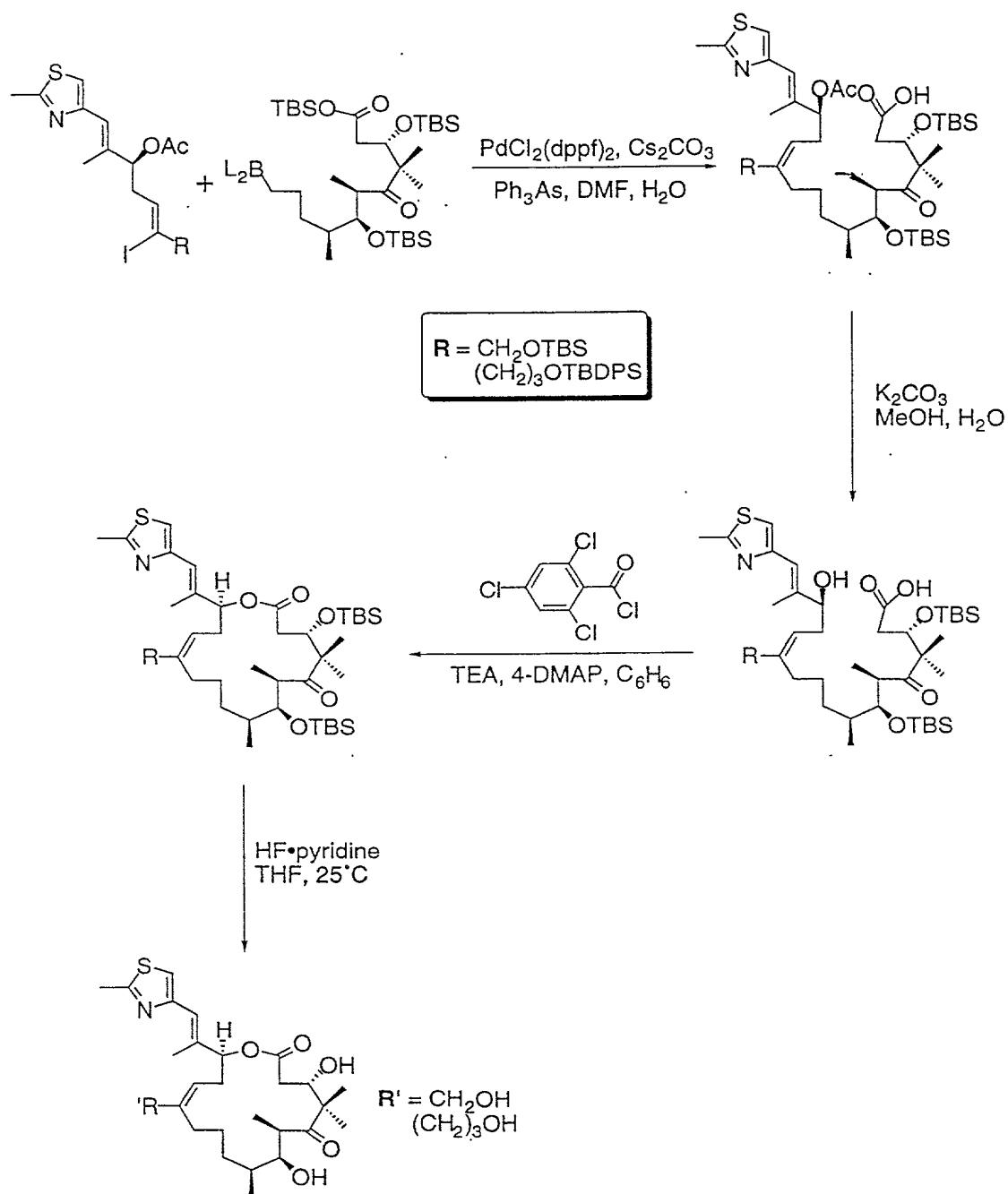


Fig. 3(B)

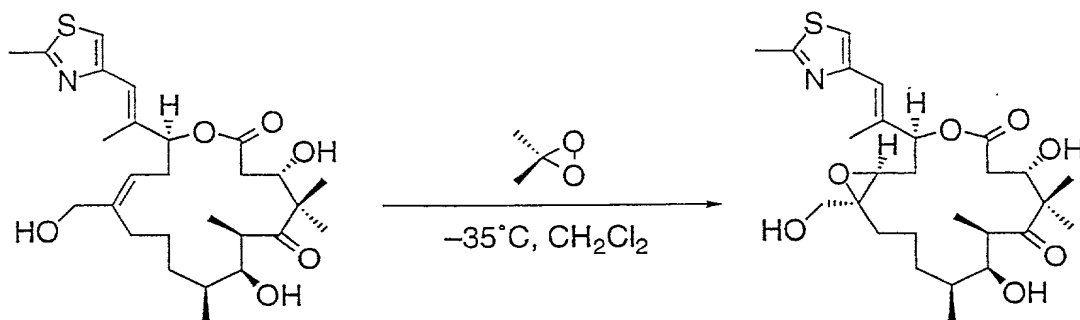
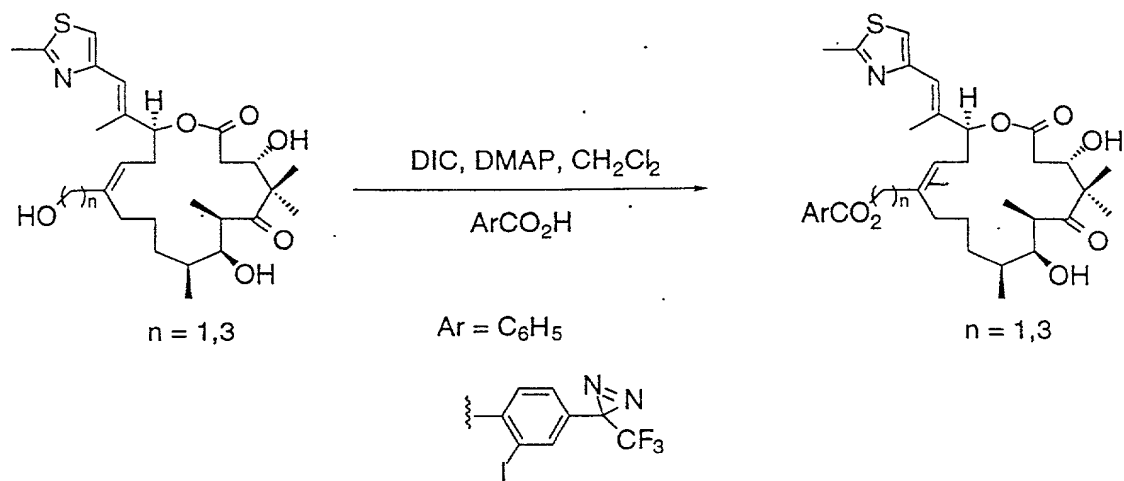
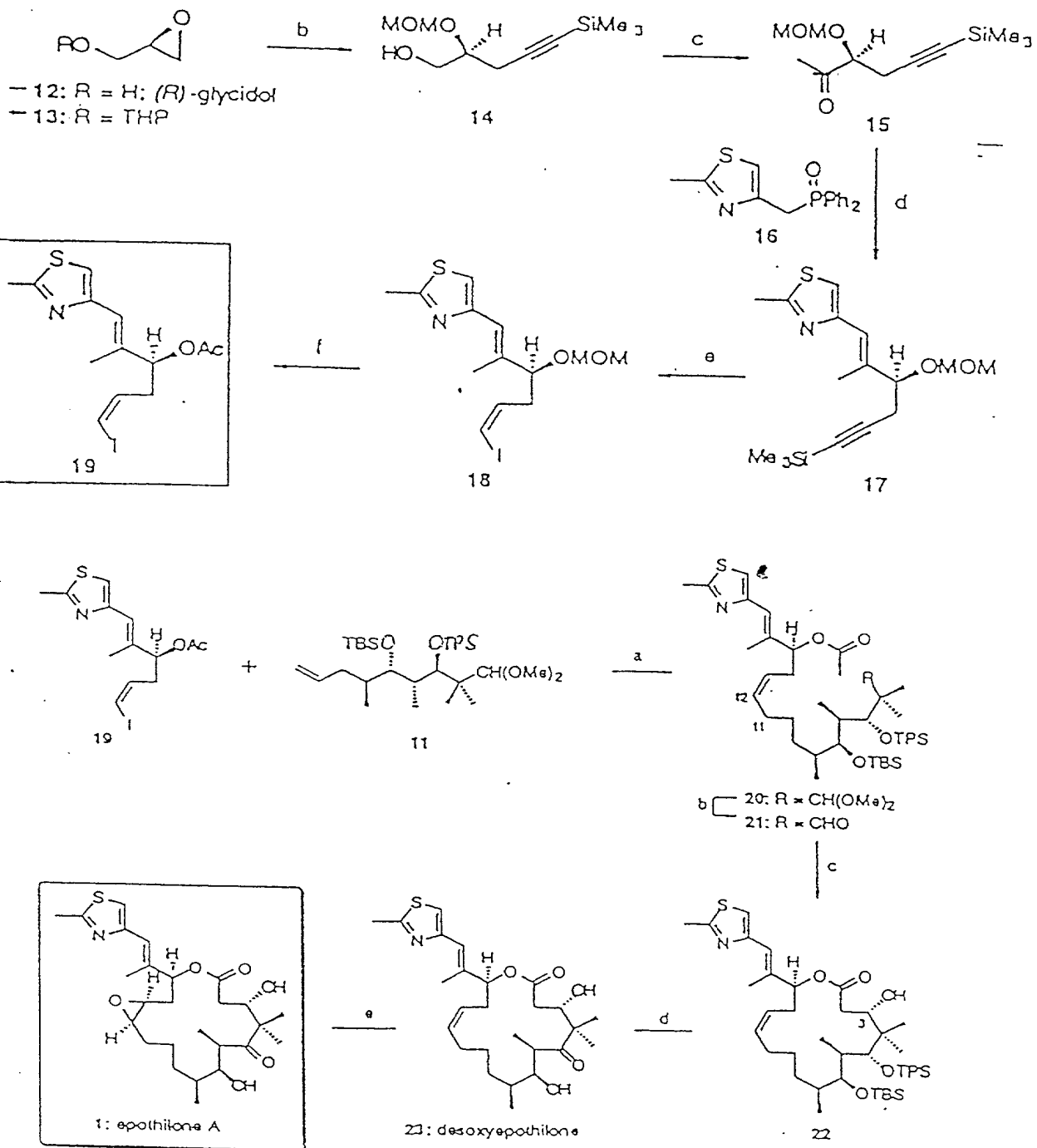
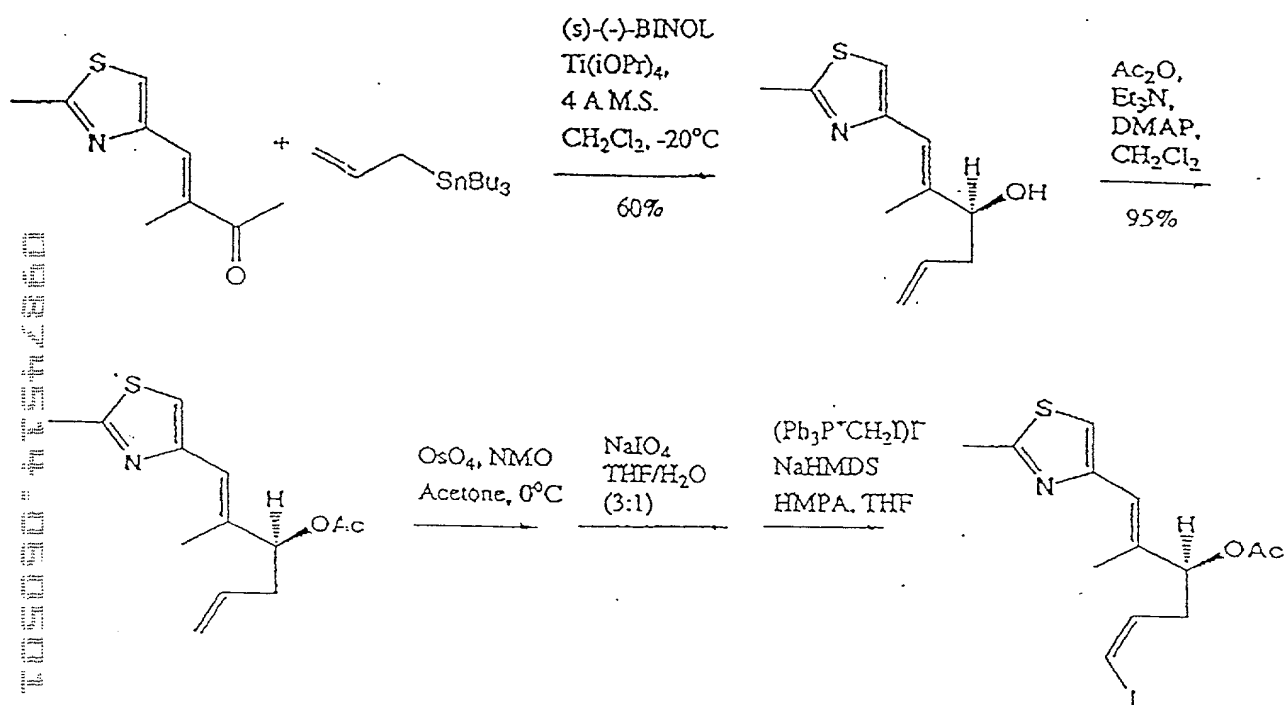


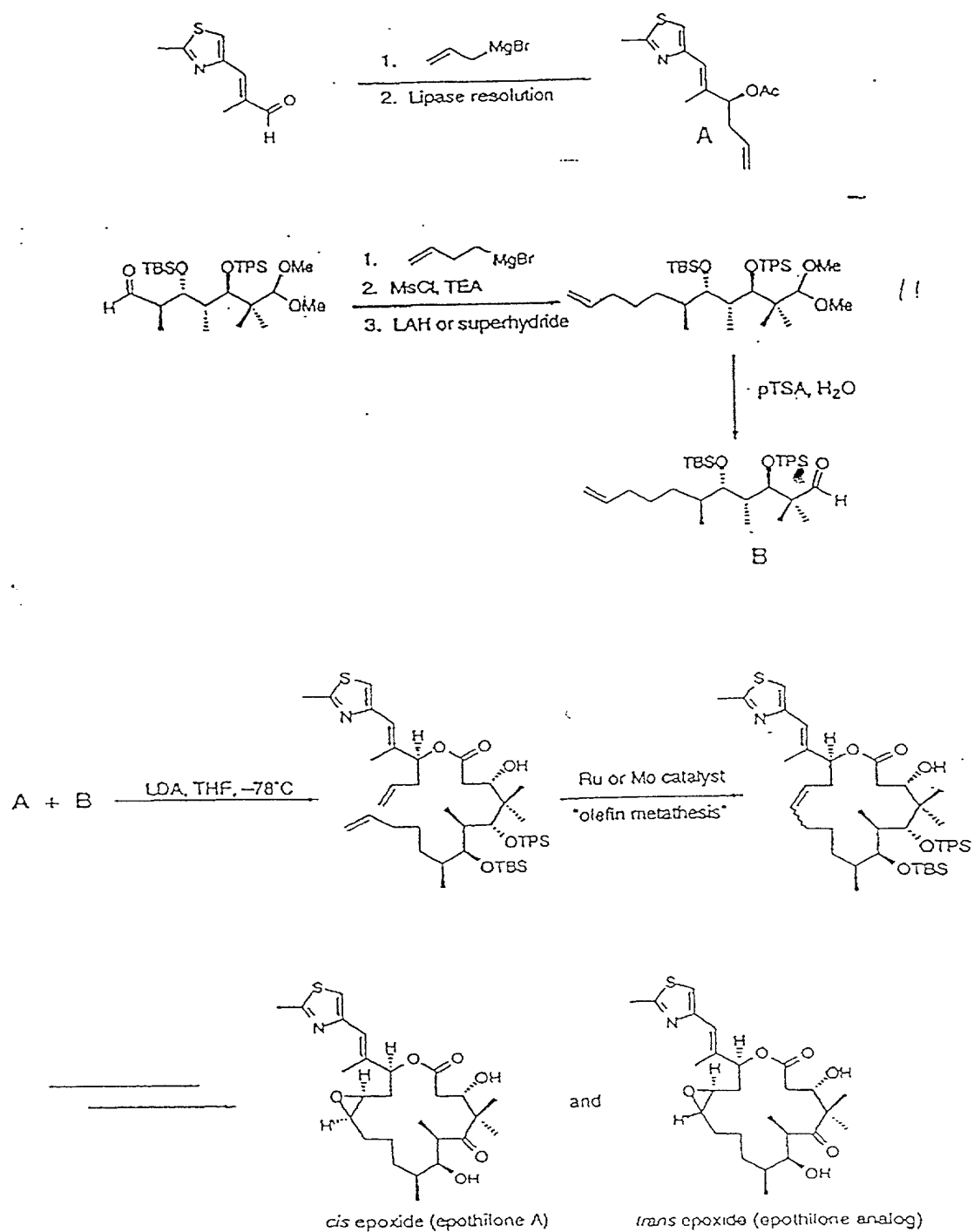
Fig. 3(C)





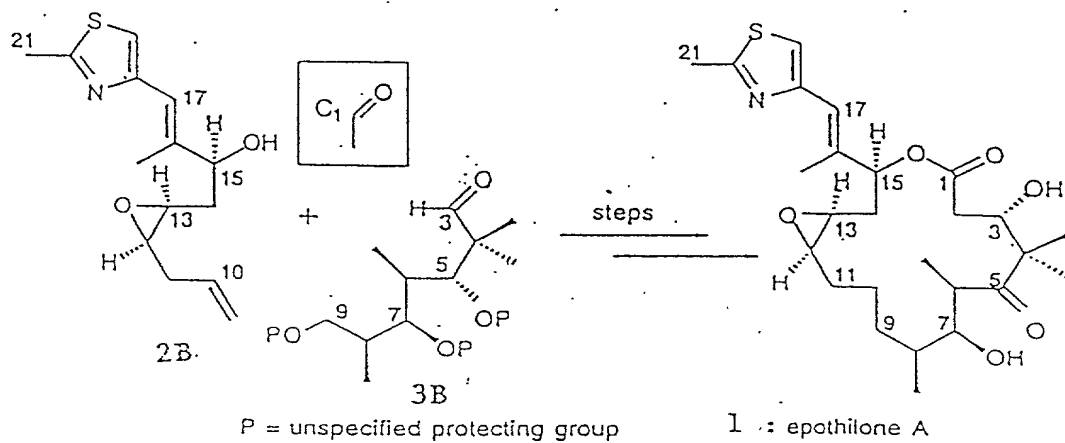
50% for three steps

Figure 5

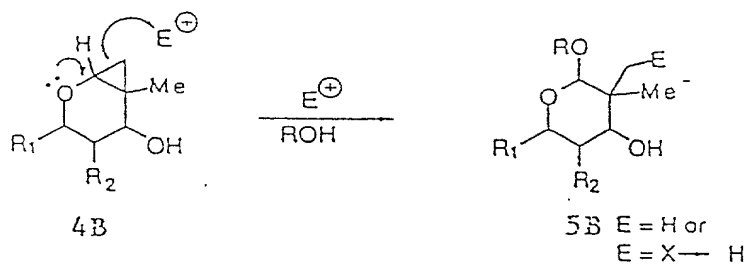


* 17 steps from known starting materials vs. 27 steps for aldol macrocyclization

Figure 6



Convergent strategy for a total synthesis of epothilone A (1).



The glycol cyclopropane solvolysis strategy for the introduction of geminal methyl groups.

Figure 7

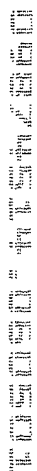
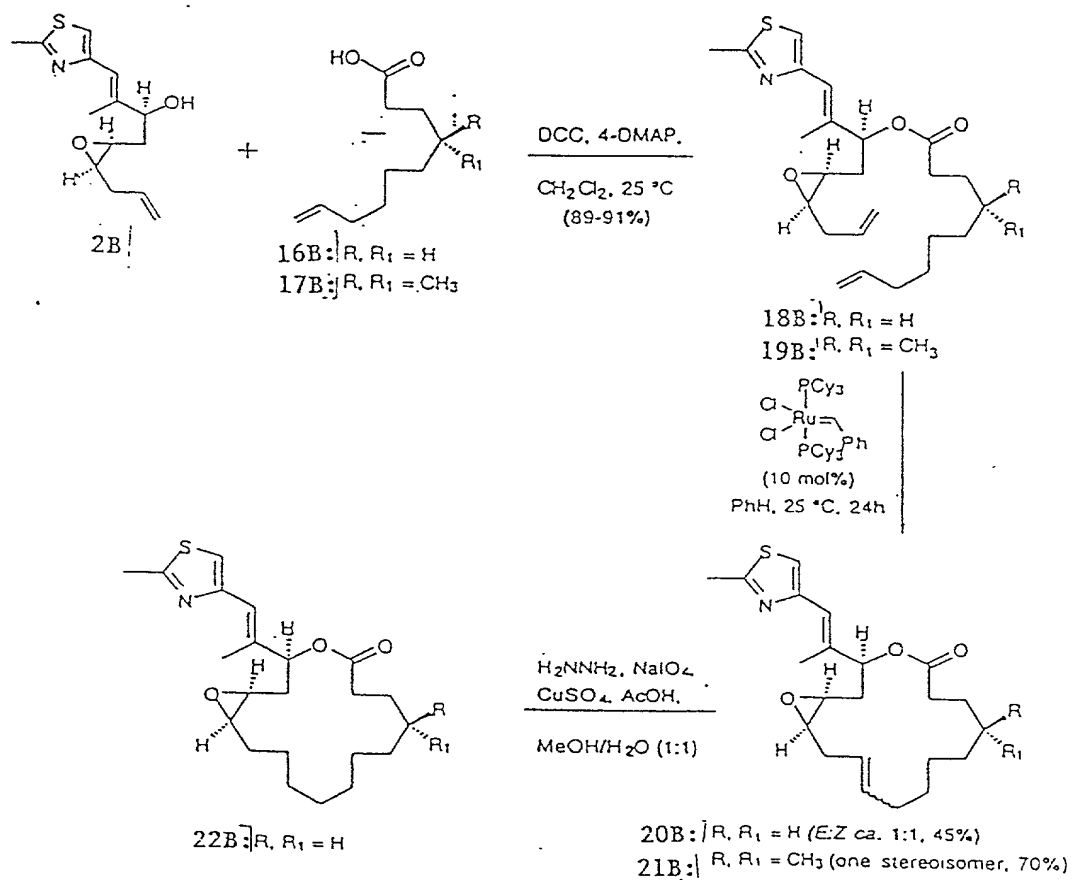


Figure 8



Construction of epothilone model systems 20^B, 21^B, and 22^B by ring-closing olefin metathesis

Figure 9

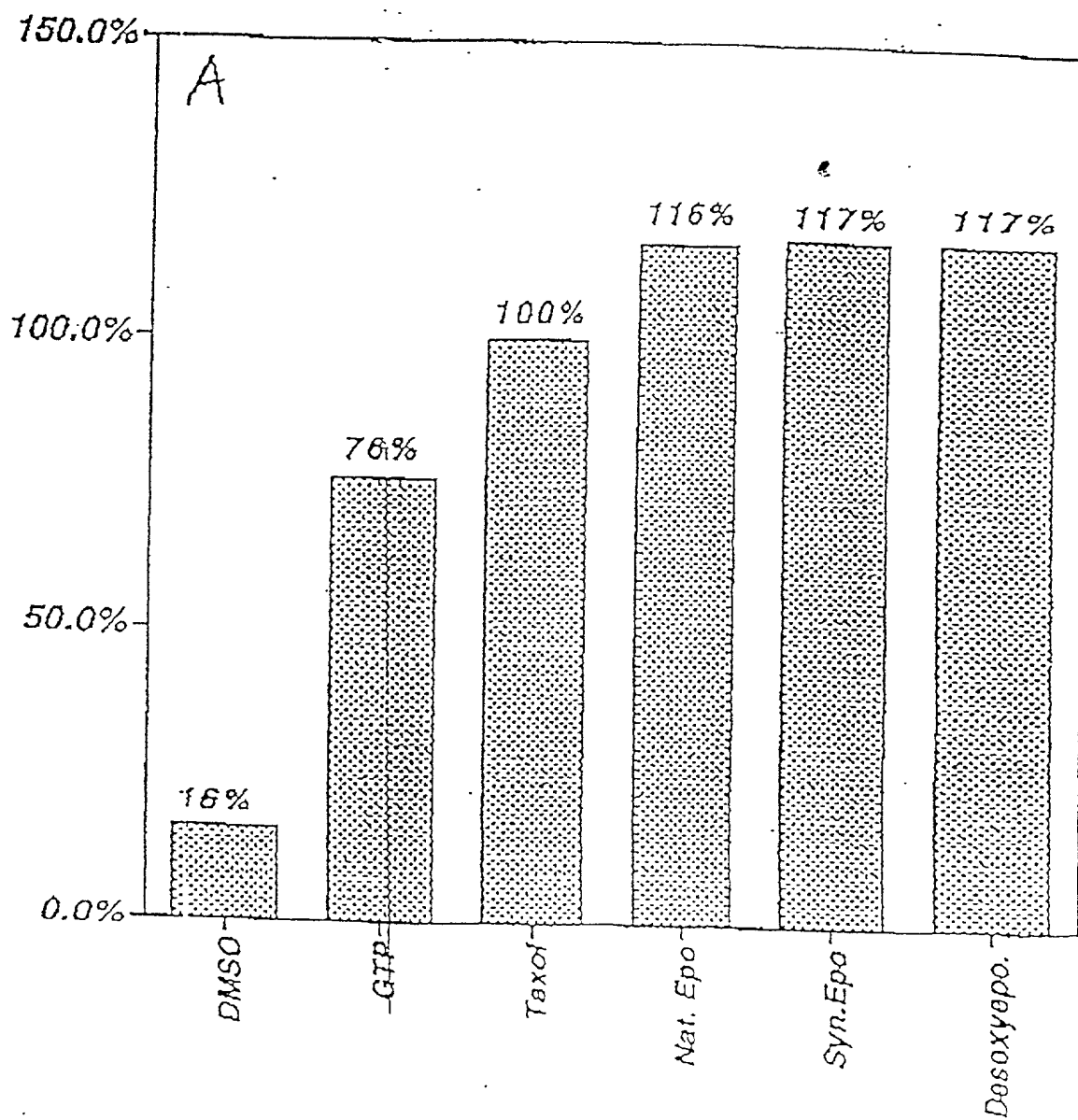


Figure 10

105000-115000

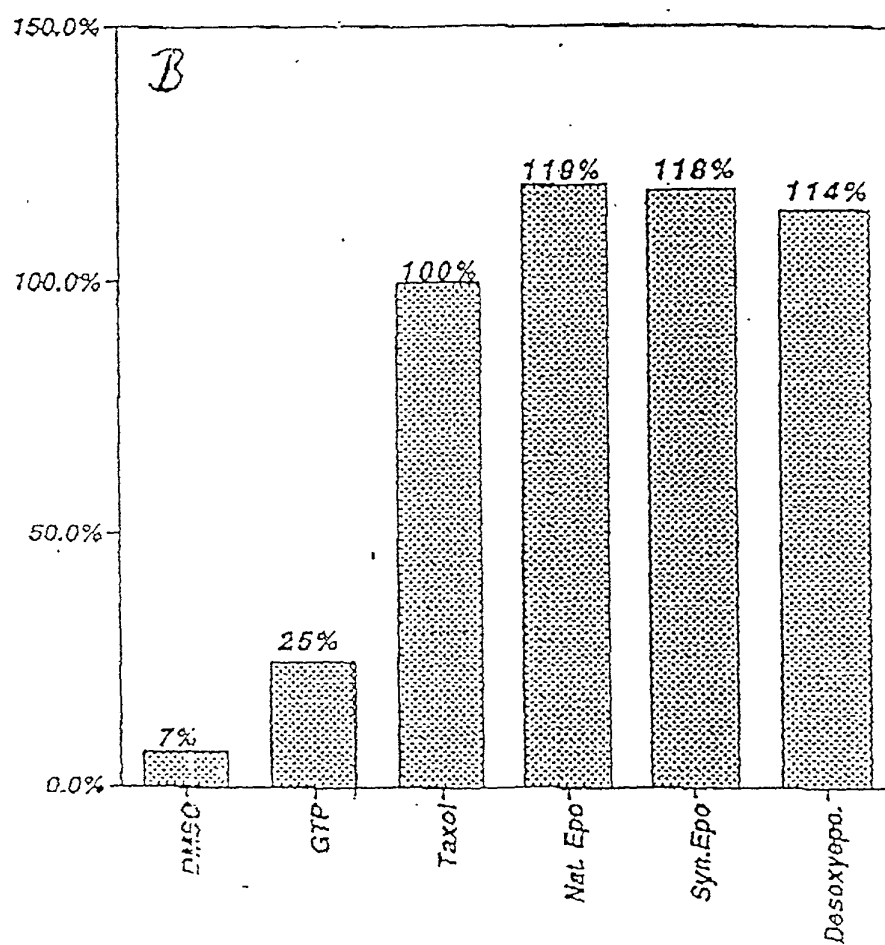
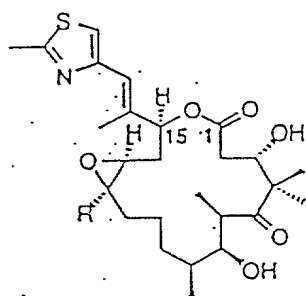
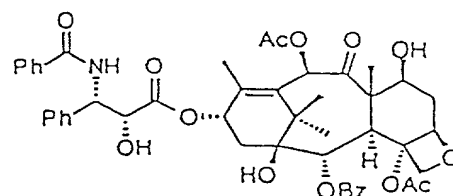


Figure 11



(A)

R = H; epothilone A
R = CH₃; epothilone B



(B)

1A: taxol™

Figure 12

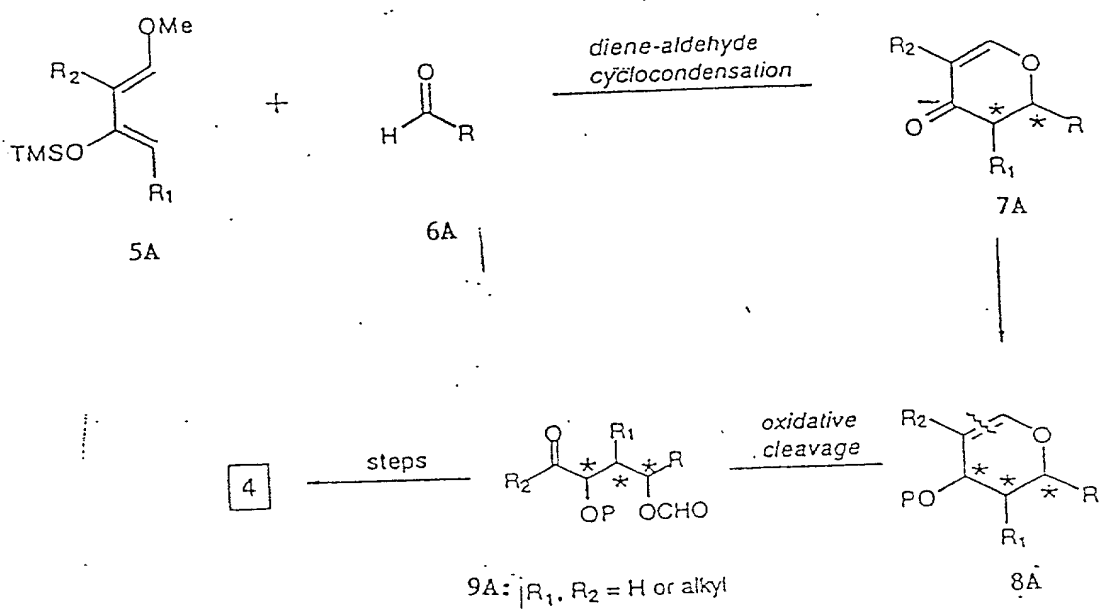


Figure 13

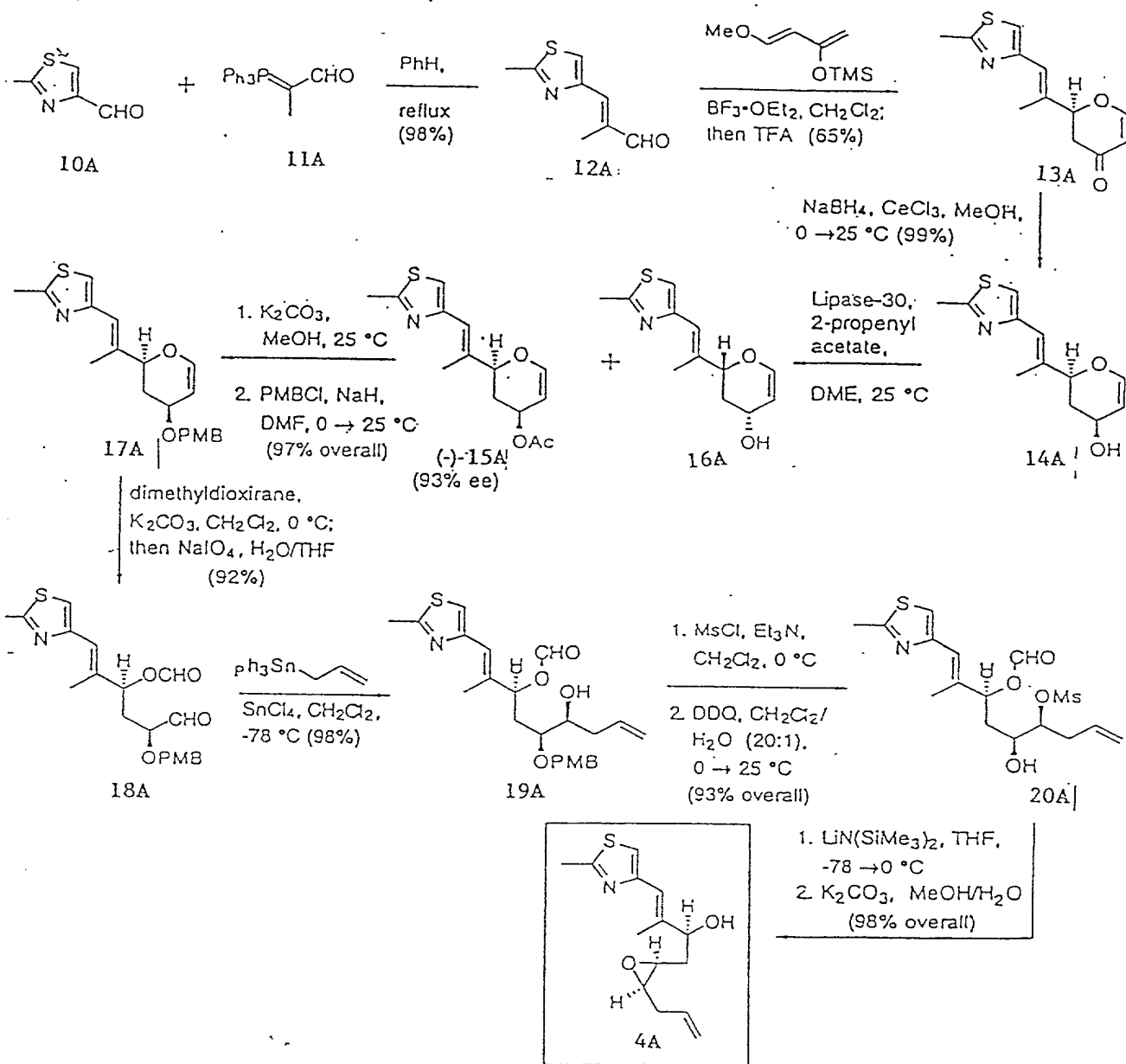
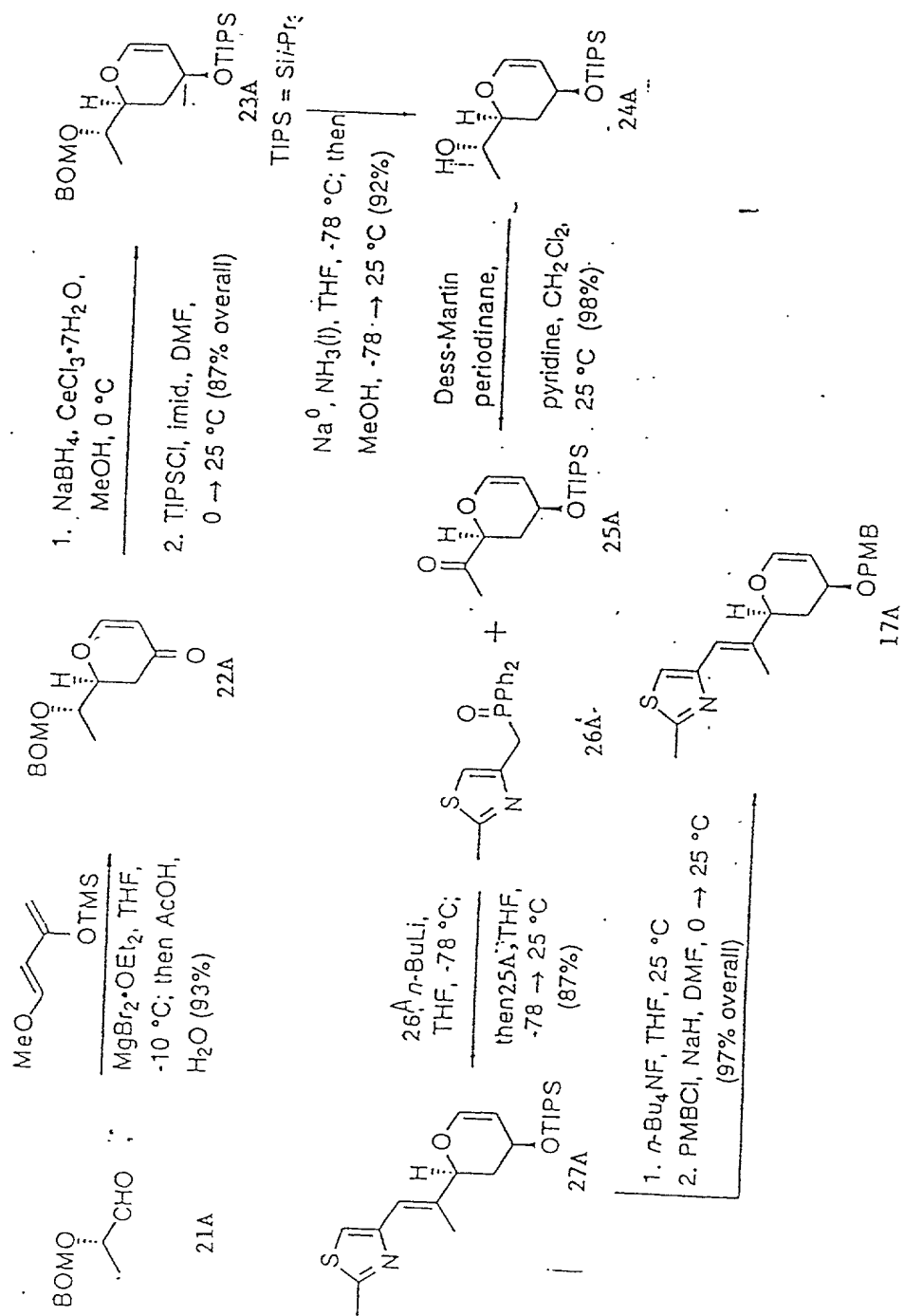


Figure 14



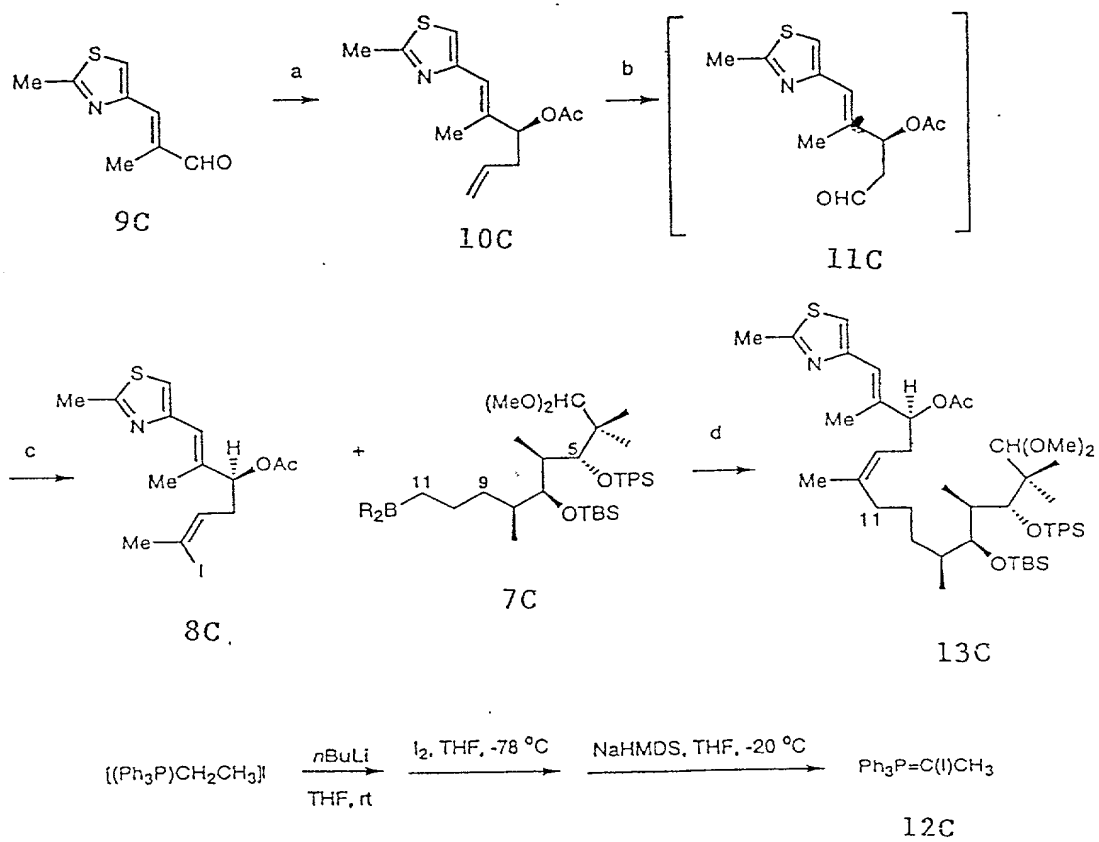


Figure 16

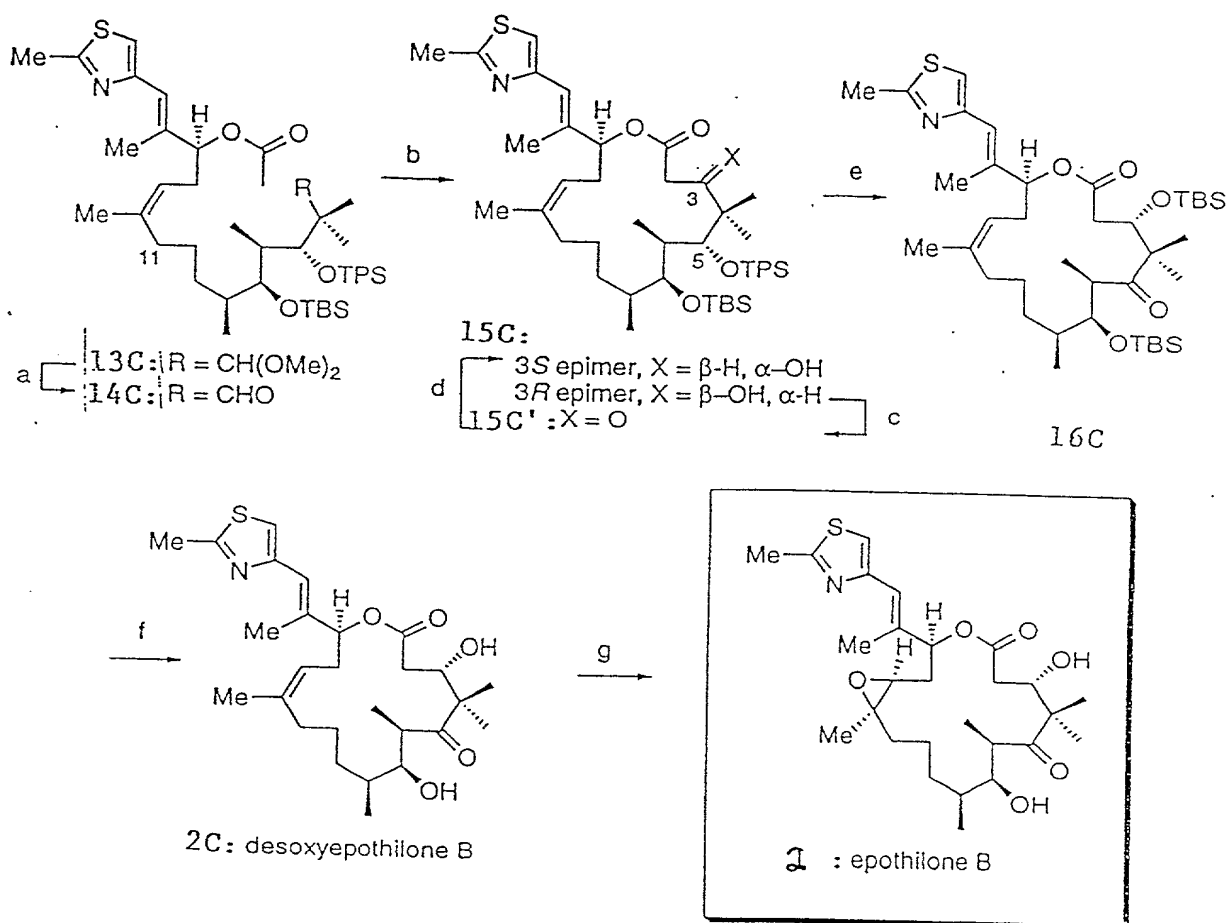


Figure 17

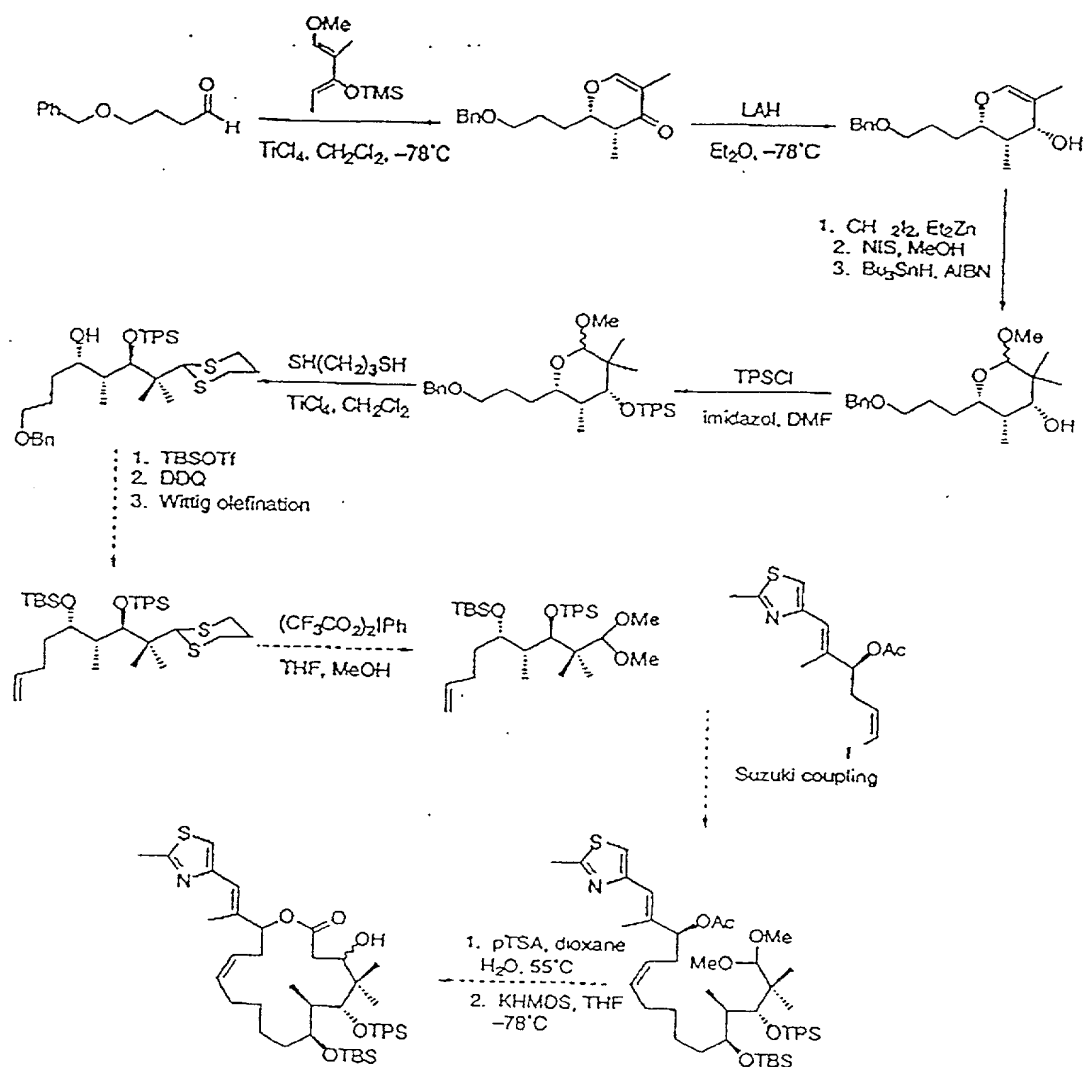


Figure 18

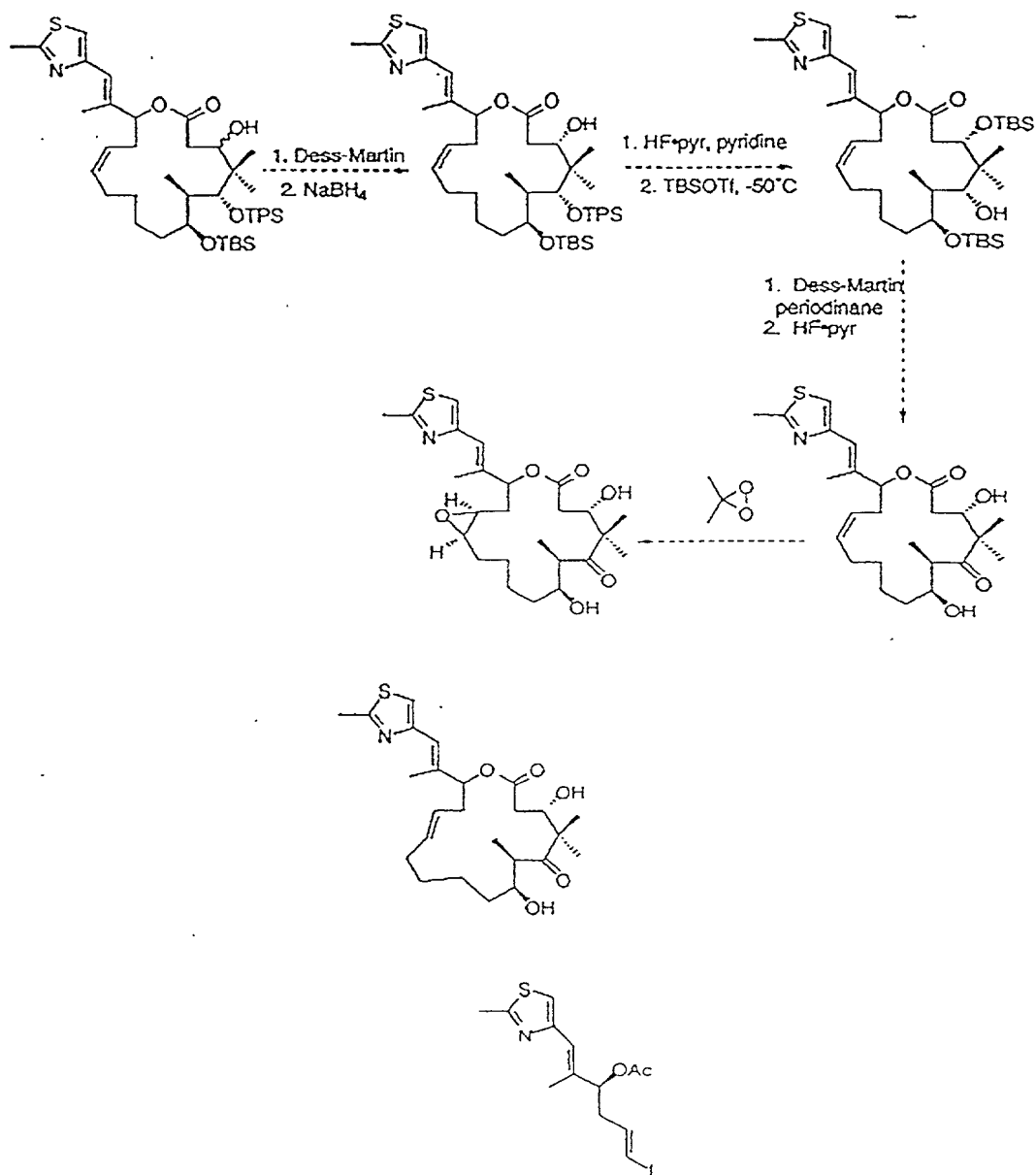


Figure 19

$R^1 = H, R^2 = \text{Me}; \text{epothilone A}$
 $R^1 = R^2 = \text{Me}; \text{epothilone B}$
 $R^1 = R^2 = H; \text{C}_8\text{-desmethyl-epothilone A (3D)}$



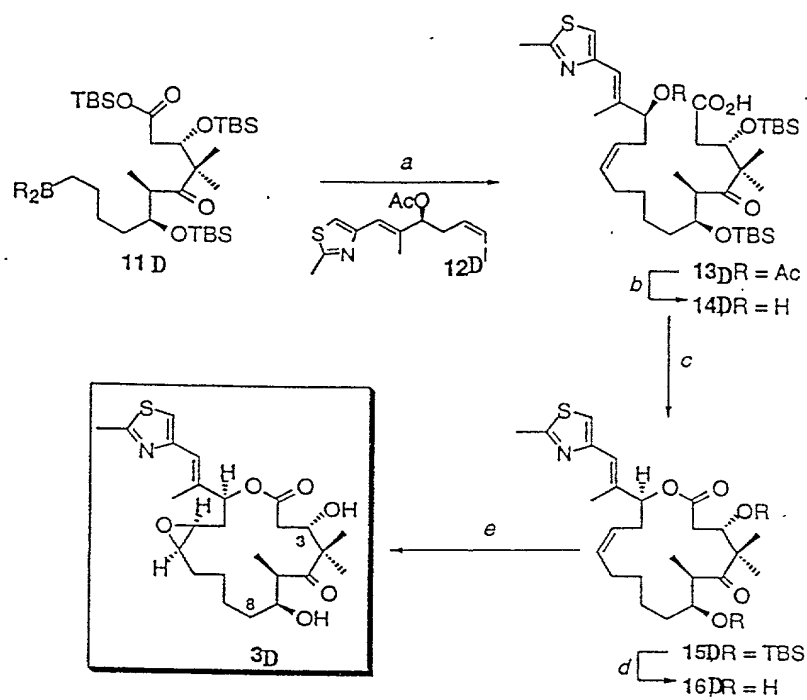


FIGURE 21

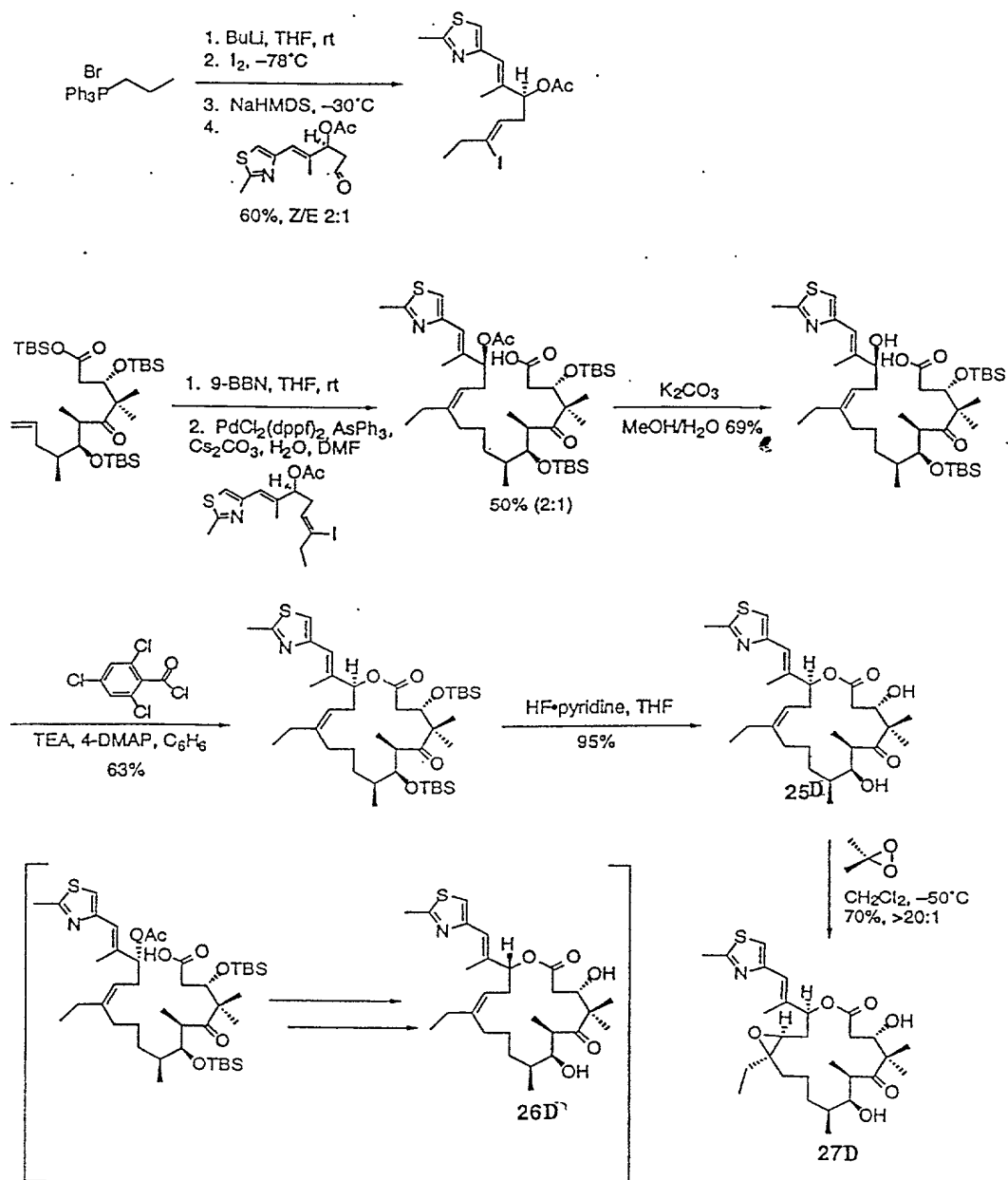


FIGURE 22

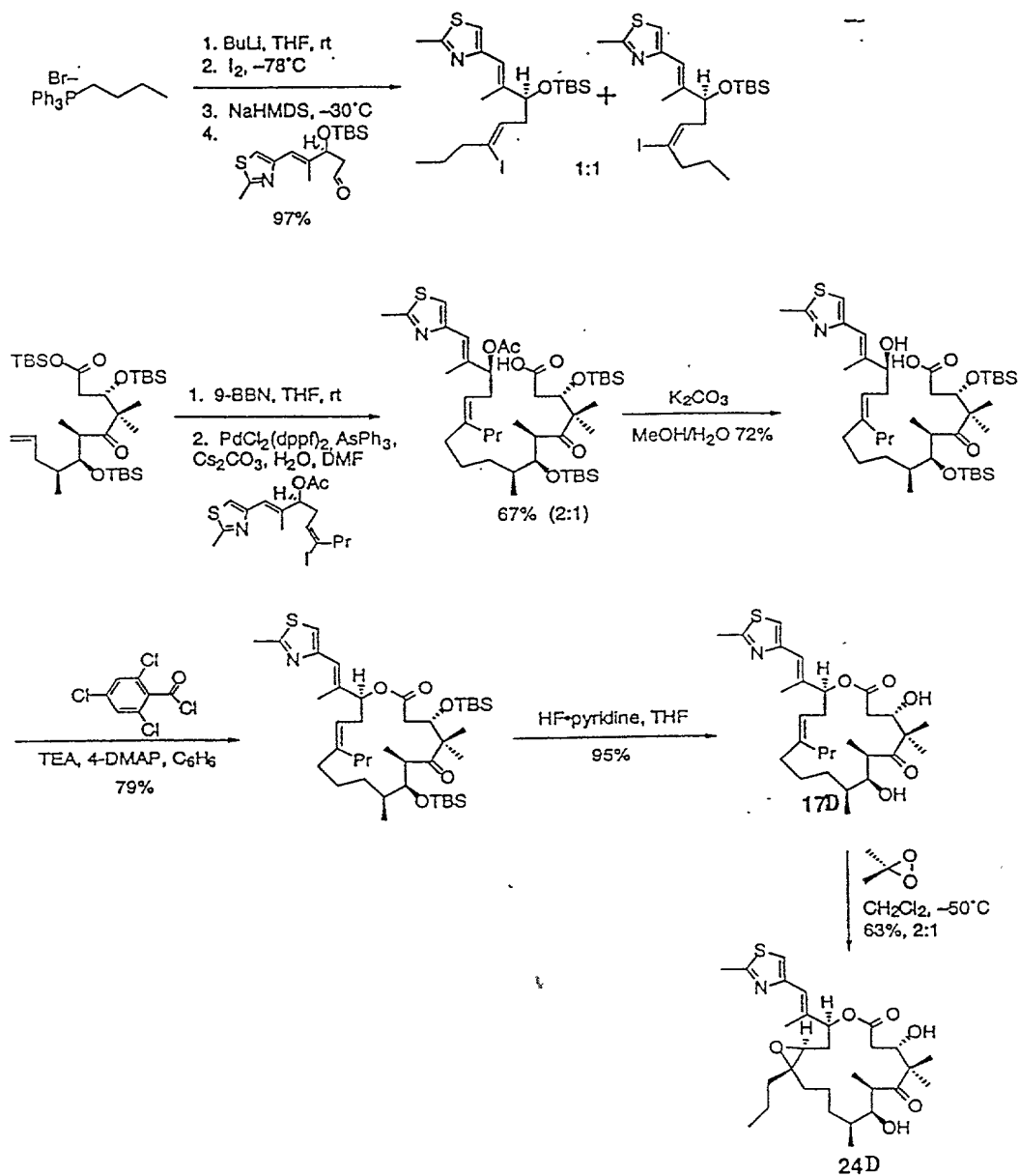


FIGURE 23

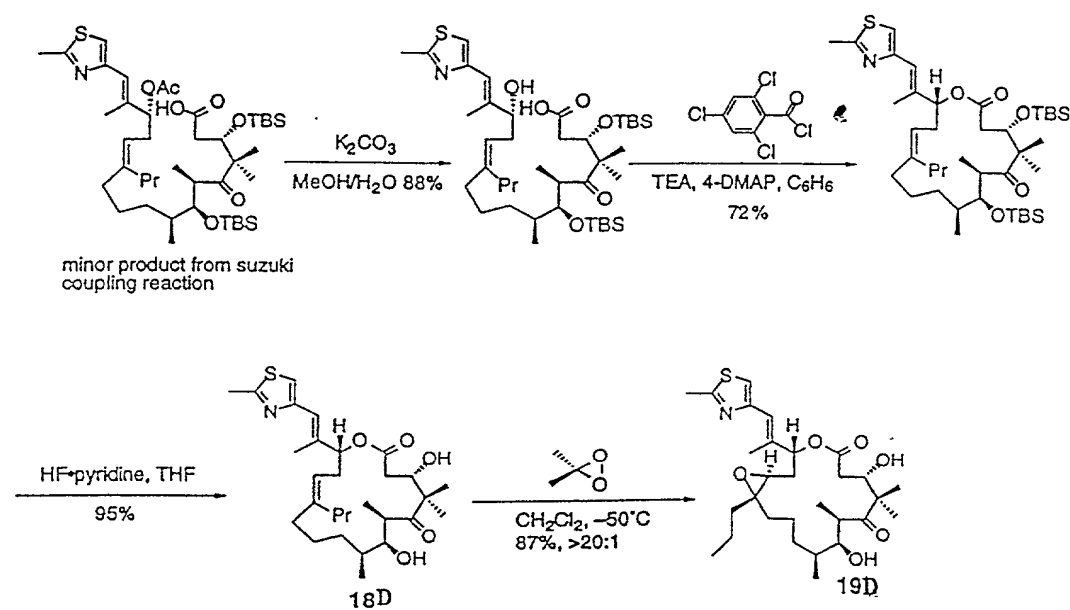


FIGURE 24

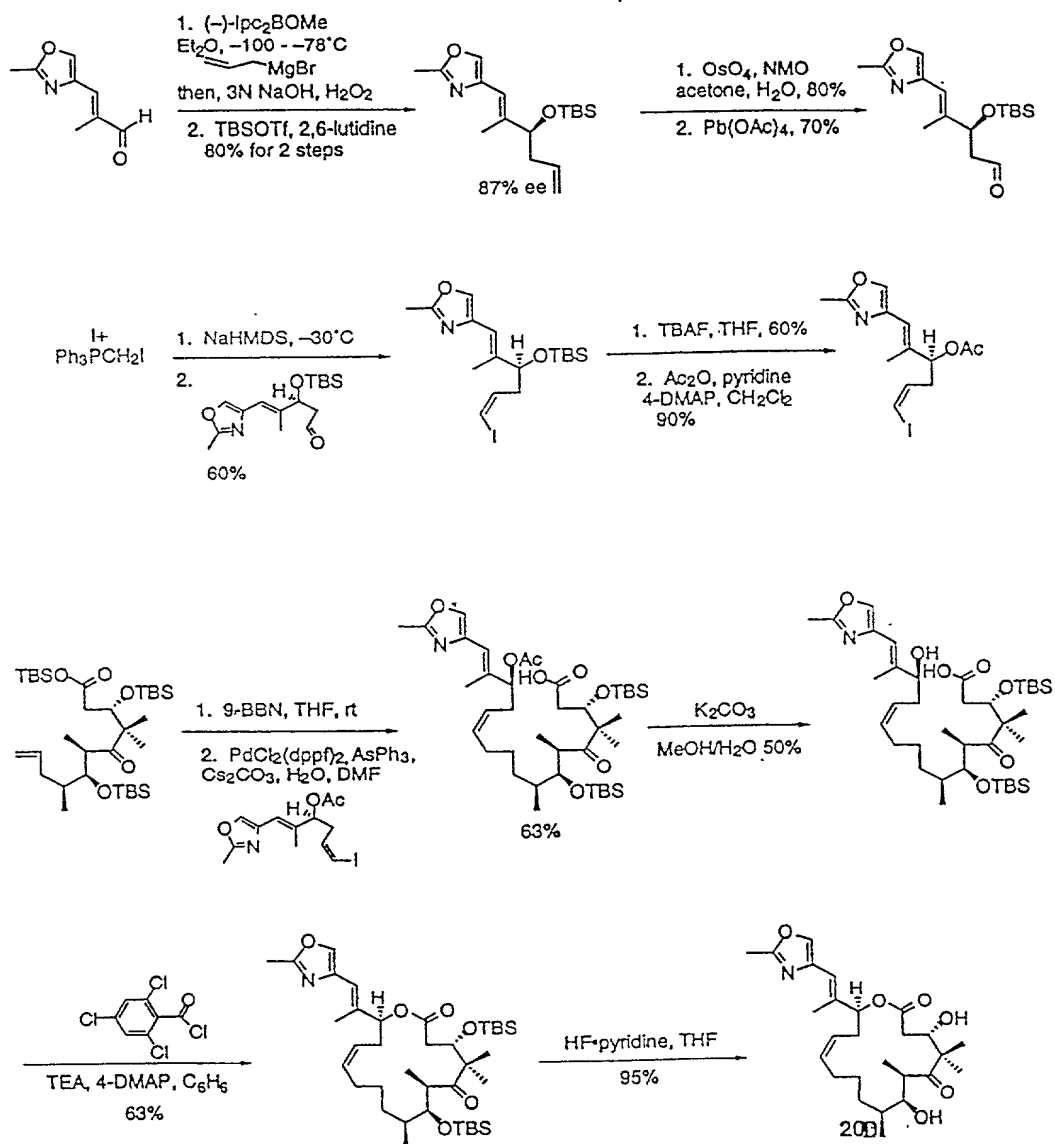


FIGURE 25

1. (-)-Ipc₂BOMe
Et₂O, -100 - -78°C
then, 3N NaOH, H₂O₂, 80%
2. Ac₂O, pyridine
4-DMAP, CH₂Cl₂
99%

87% ee

1. AD-mix α
2. Pb(OAc)₄
30%

Ph₃P=CH-I
50%

R = H, F, CF₃
R=H is the only compound completed, F and CF₃ are nearly completed

1. 9-BBN, THF, rt
2. PdCl₂(dppf)₂, AsPh₃,
Cs₂CO₃, H₂O, DMF
50%

K₂CO₃
MeOH/H₂O 85%

TEA, 4-DMAP, C₆H₅
50%

HF·pyridine, THF
10%

22D. (R = H)

FIGURE 26

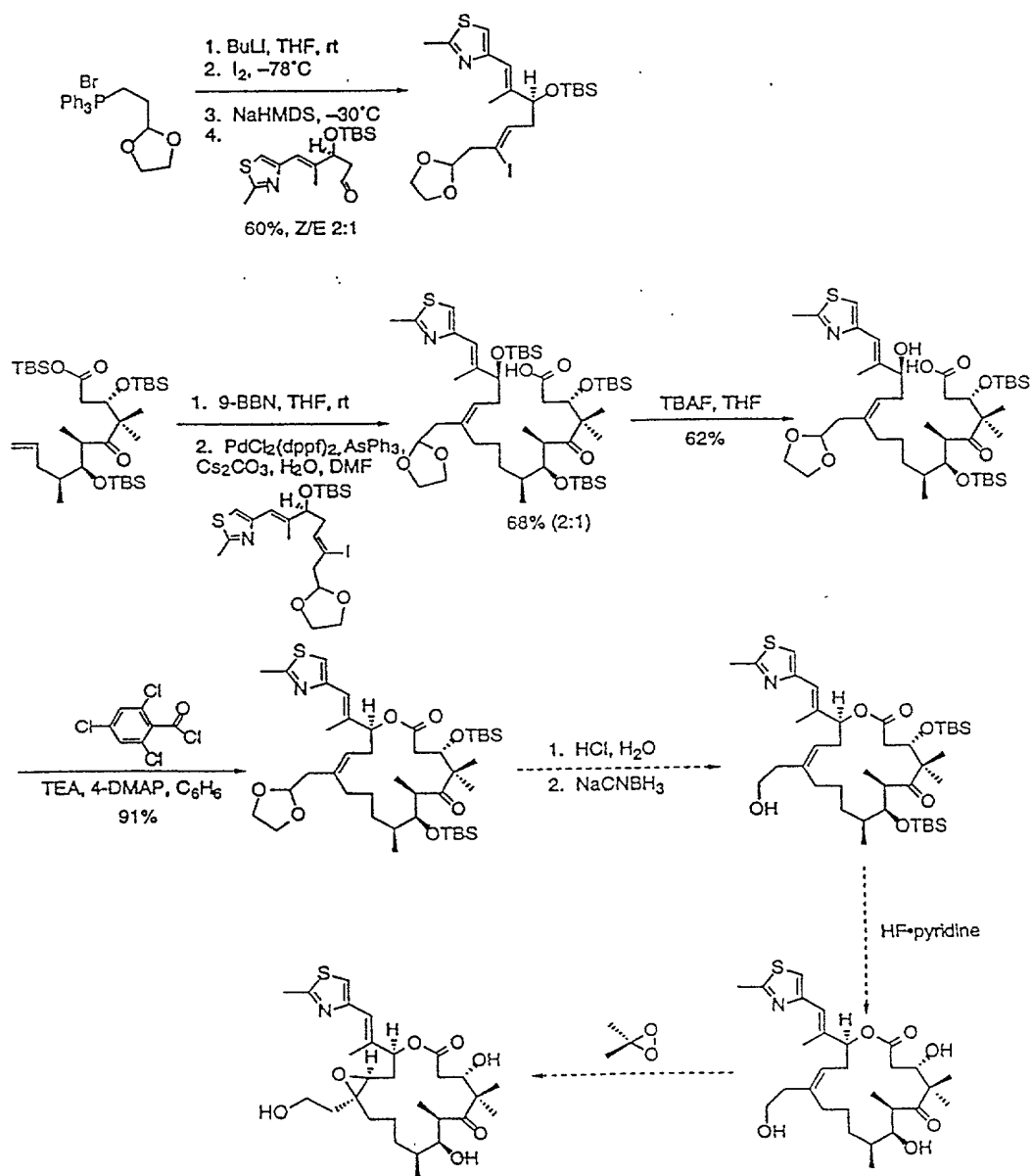


FIGURE 27

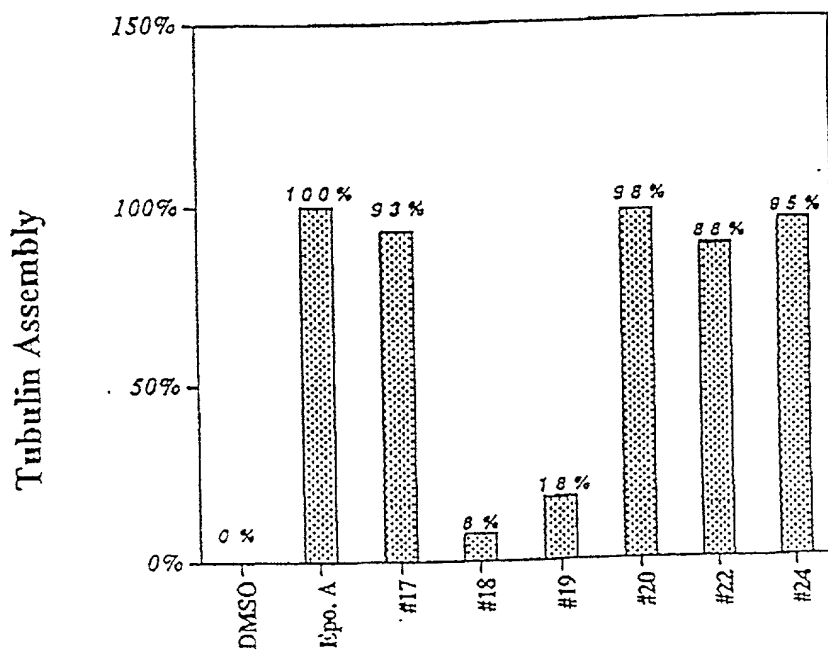
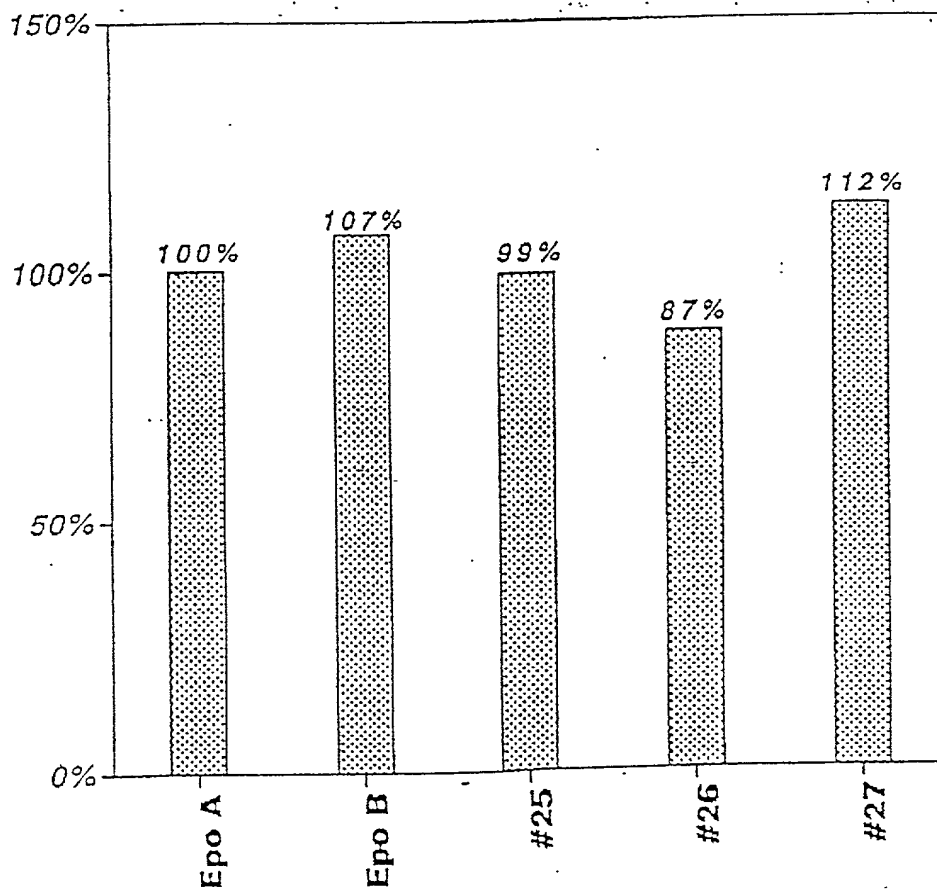


FIGURE 28

17

Cc1cc(C/C=C/[C@H]2CC[C@@H]3[C@@H](C)[C@H](O)[C@@H](C)[C@H]3C(=O)C[C@H]2C(=O)O)cc1

0.8786
0.0398
1.0000
0.9429
1.0108
1.0185
0.9643
1.9341
0.9504
3.0668
4.0583
0.9632
2.9612
3.1931
2.1296
3.3354
3.3220
3.1635
2.9472
4.0402
3.4568

17

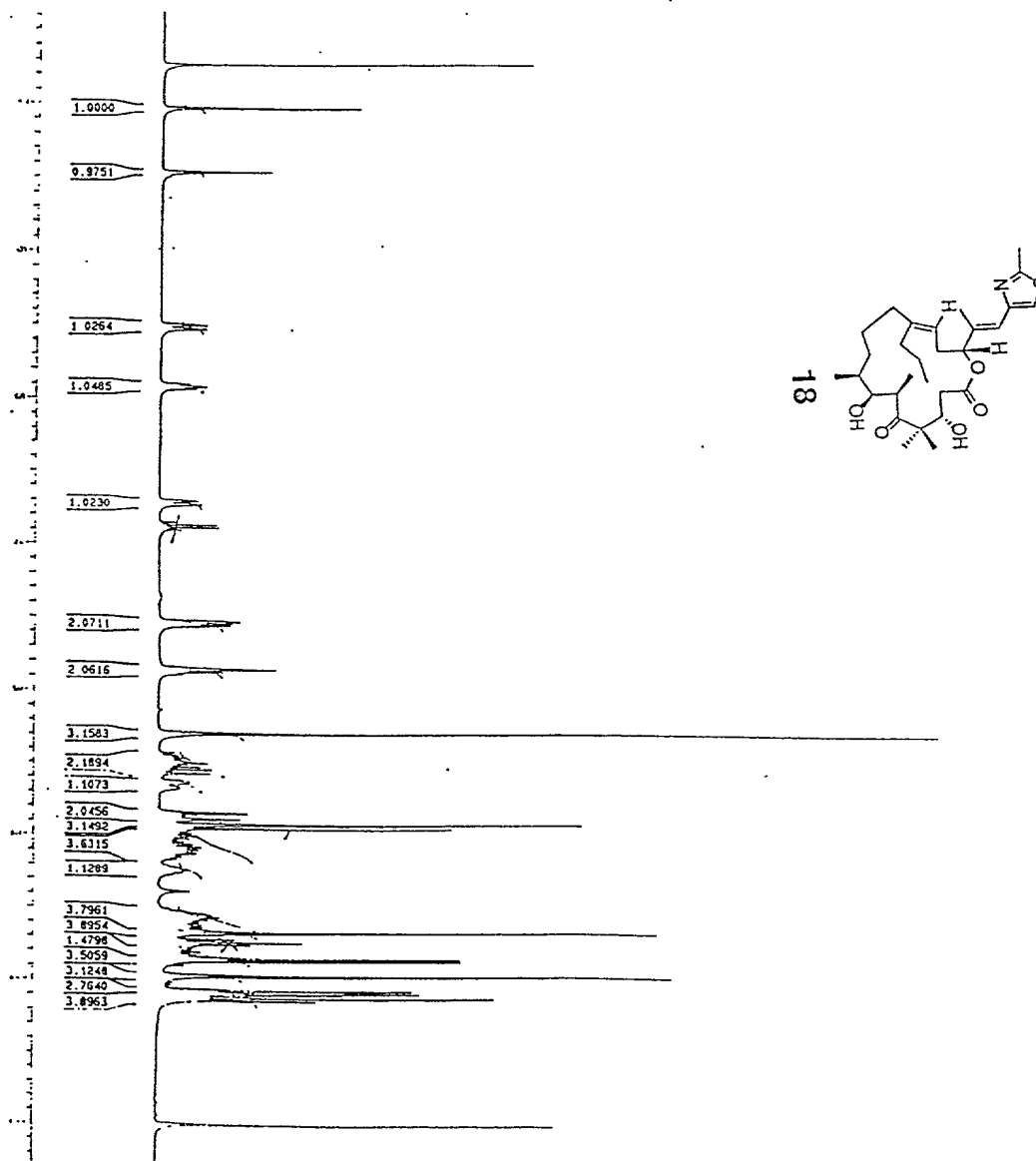


FIGURE 30

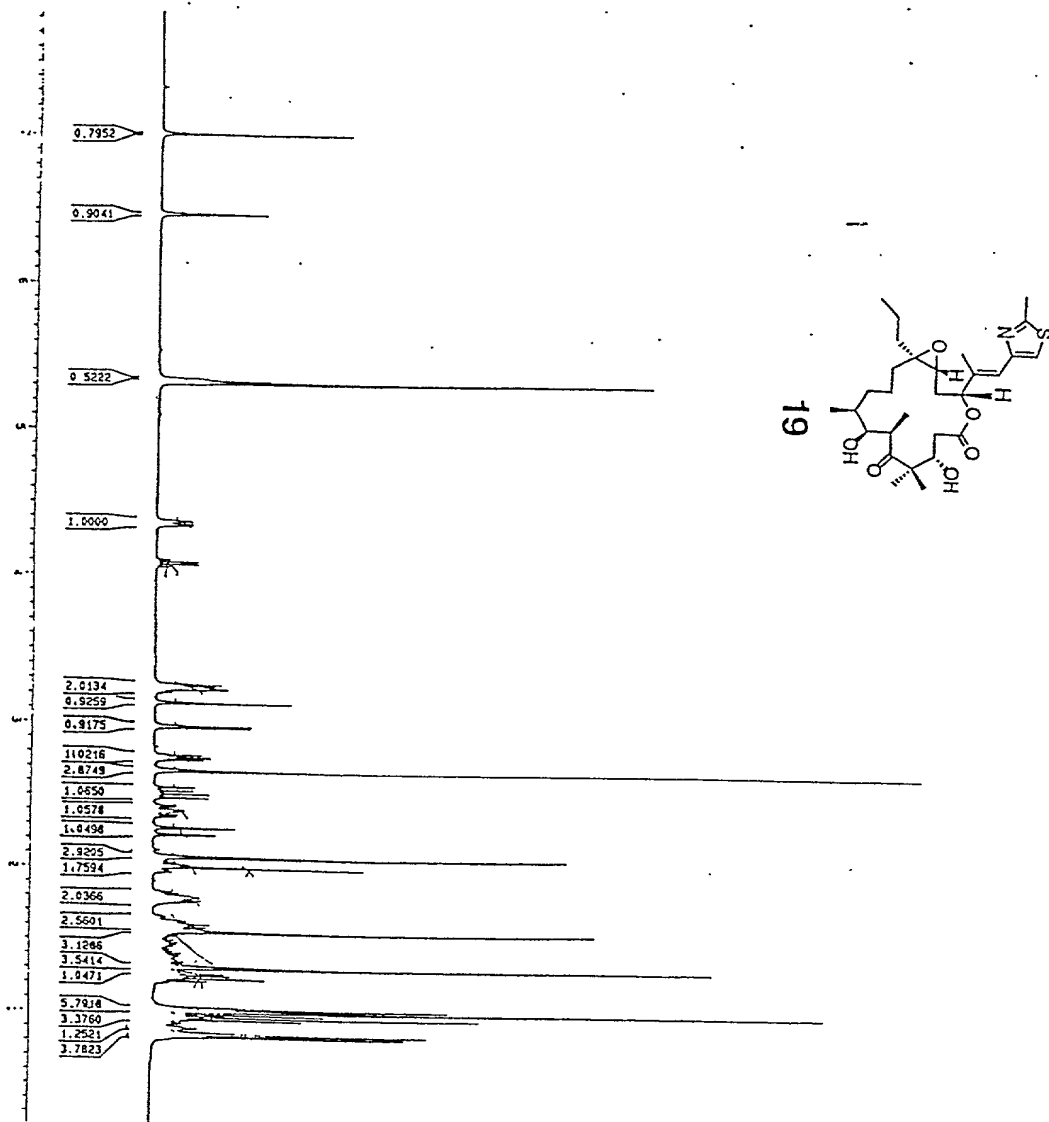


FIGURE 31

Chemical structure of compound 20 is shown in the center of the spectrum.

Chemical Shifts (ppm):

- 7.5000
- 6.5000
- 6.0000
- 5.5000
- 5.0000
- 4.5000
- 4.0000
- 3.5000
- 3.0000
- 2.5000
- 2.0000
- 1.5000
- 1.0000
- 0.5000
- 0.0000

Integration Values:

- 1.0000
- 1.0109
- 3.2652
- 1.6368
- 1.0787
- 2.8911
- 1.2693
- 6.1035
- 2.6089
- 5.5207
- 2.6680
- 5.0318
- 8.3306
- 3.3759
- 3.7195

Peak Labels (ppm):

- 2993.90
- 2905.00
- 2532.71
- 2186.48
- 2182.23
- 2176.17
- 2171.74
- 2165.82
- 2161.92
- 2157.51
- 2152.88
- 2143.01
- 2147.82
- 2137.16
- 2132.48
- 2121.74
- 2112.52
- 1676.47
- 1665.90
- 1656.48
- 1649.31
- 1642.19
- 1635.04
- 1489.99
- 1251.79
- 1244.96
- 1236.16
- 1223.93
- 1199.04
- 1078.74
- 1069.03
- 1054.03
- 1015.42
- 1001.97
- 999.95
- 984.73
- 956.08
- 951.92
- 940.68
- 938.55
- 884.11
- 815.97
- 791.67
- 781.36
- 549.99
- 544.53
- 536.38
- 527.60
- 522.05
- 507.81
- 504.93
- 500.54
- 497.99
- 493.31
- 490.92
- 482.31
- 473.79
- 467.04
- 438.02
- 430.70
- 424.75
- 398.95
- 391.99

20



FIGURE 33

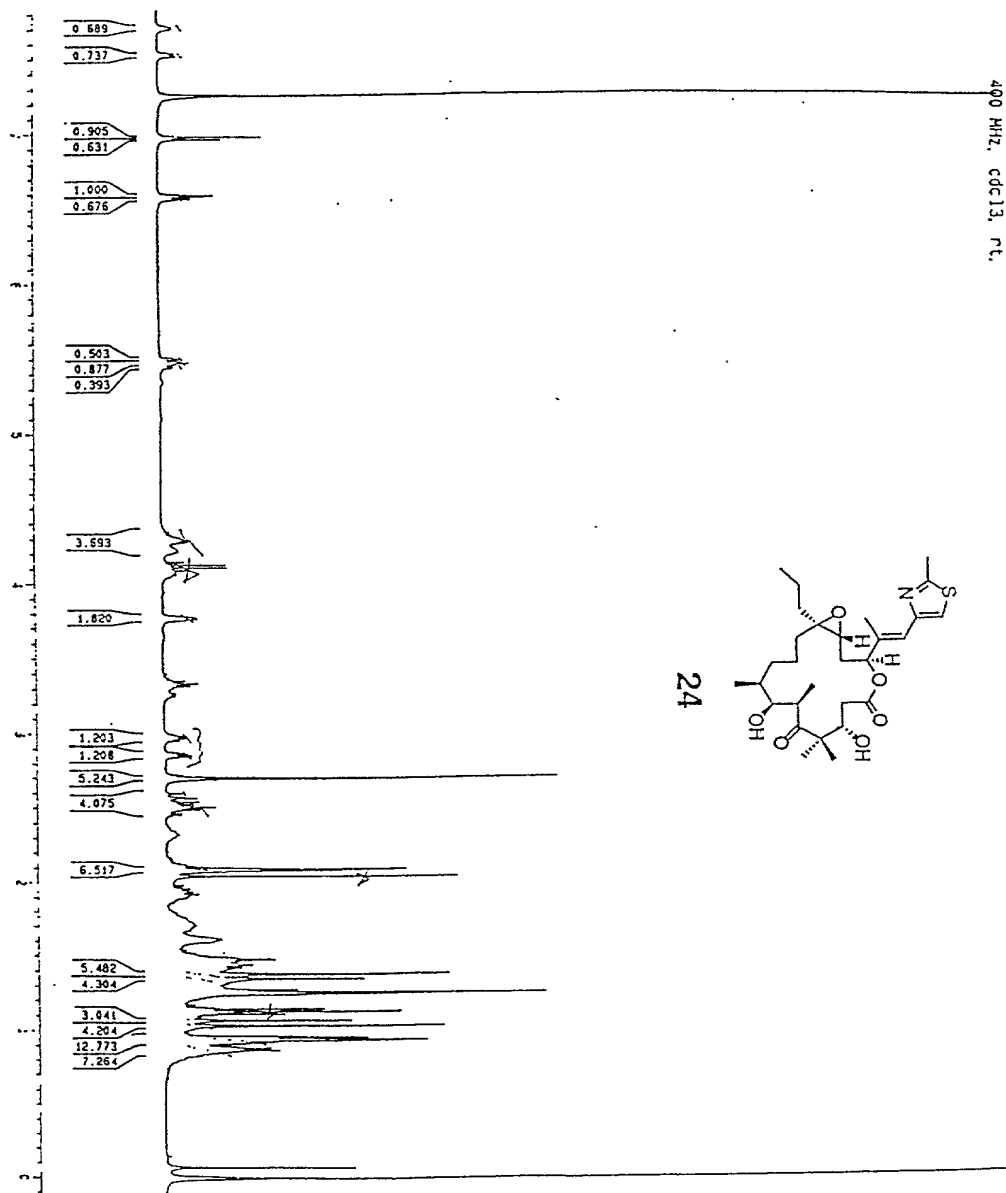


FIGURE 34

DSS-11-135-1

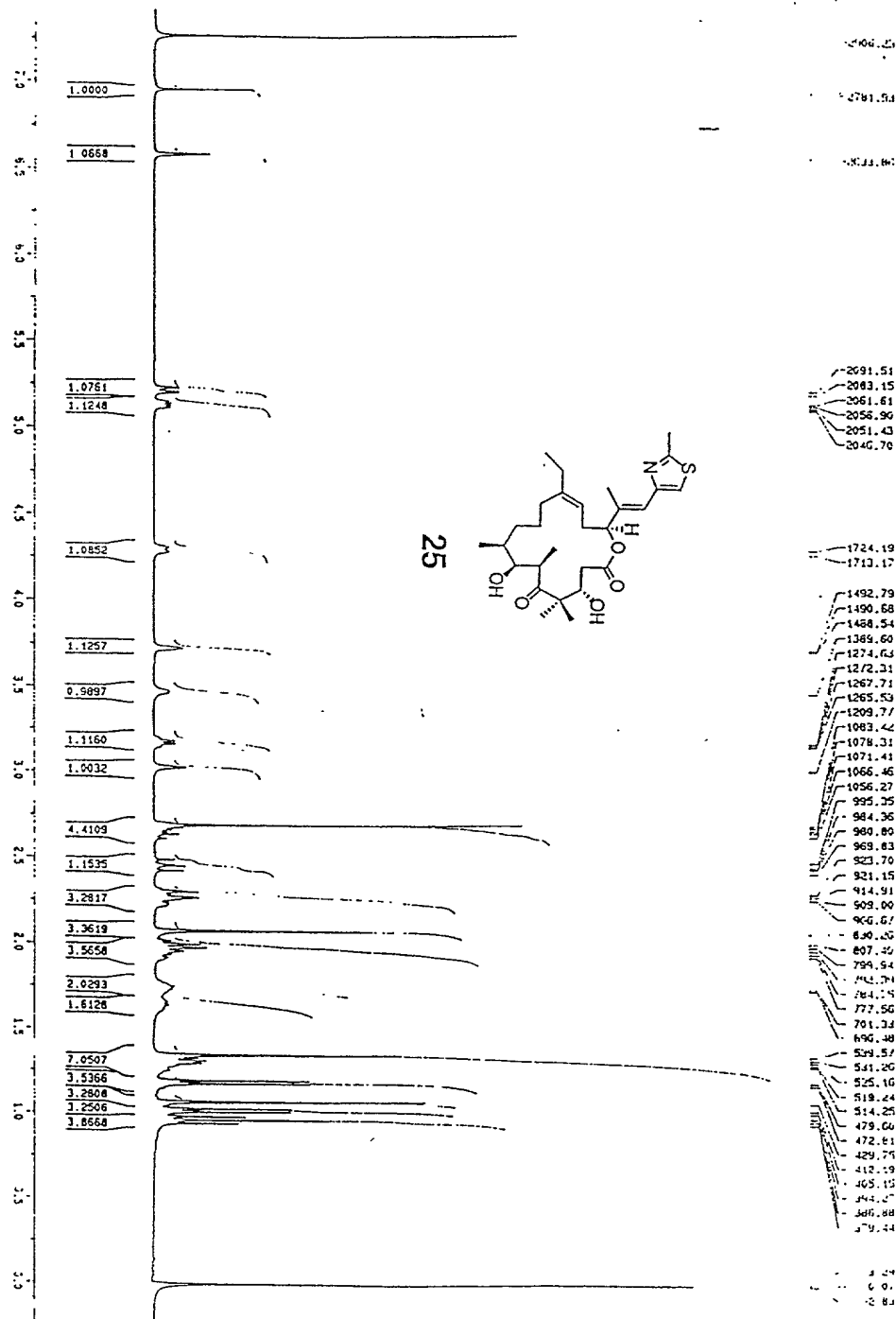


FIGURE 35

DSS-II-138-11

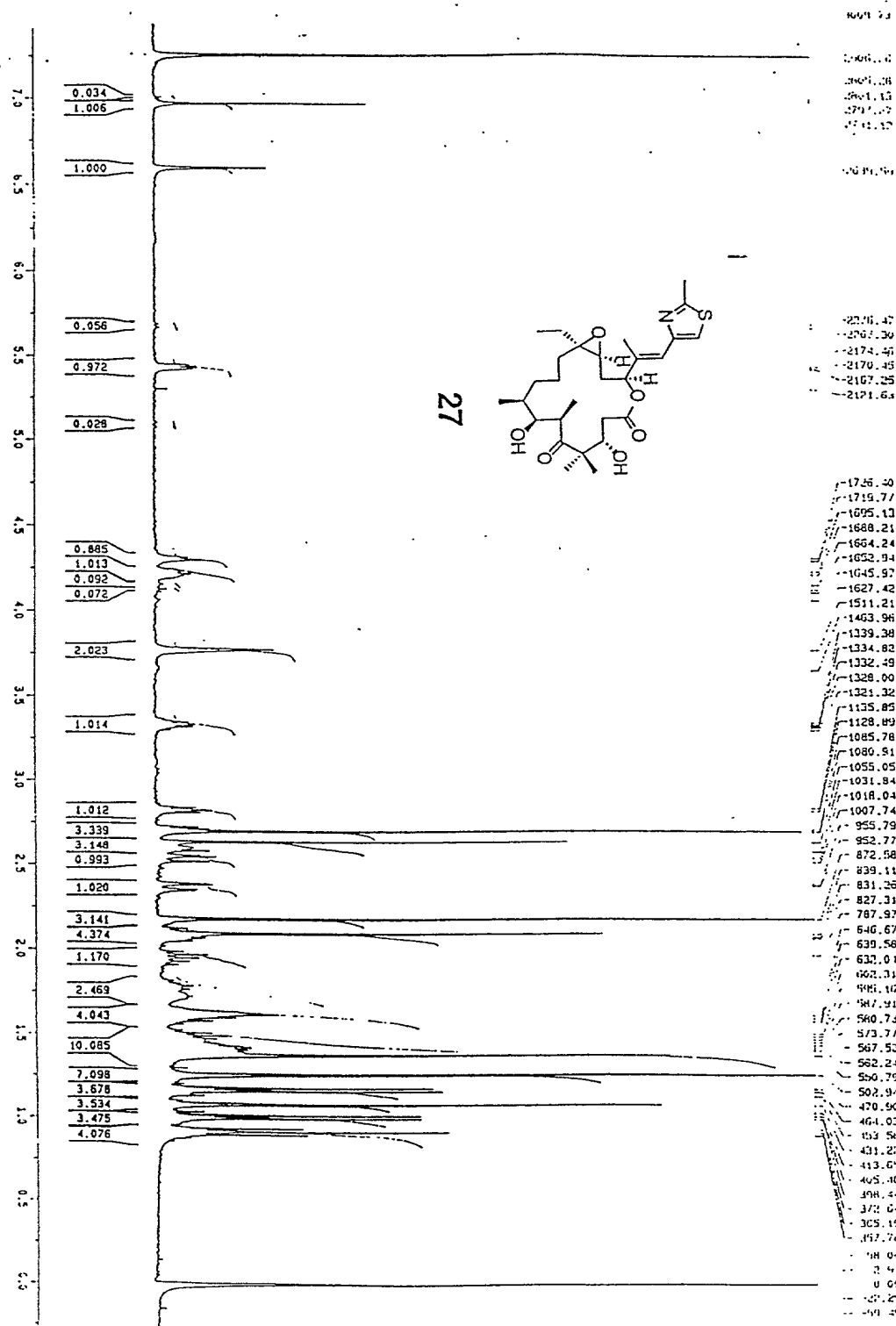


FIGURE 37

COMBINATION INDEX

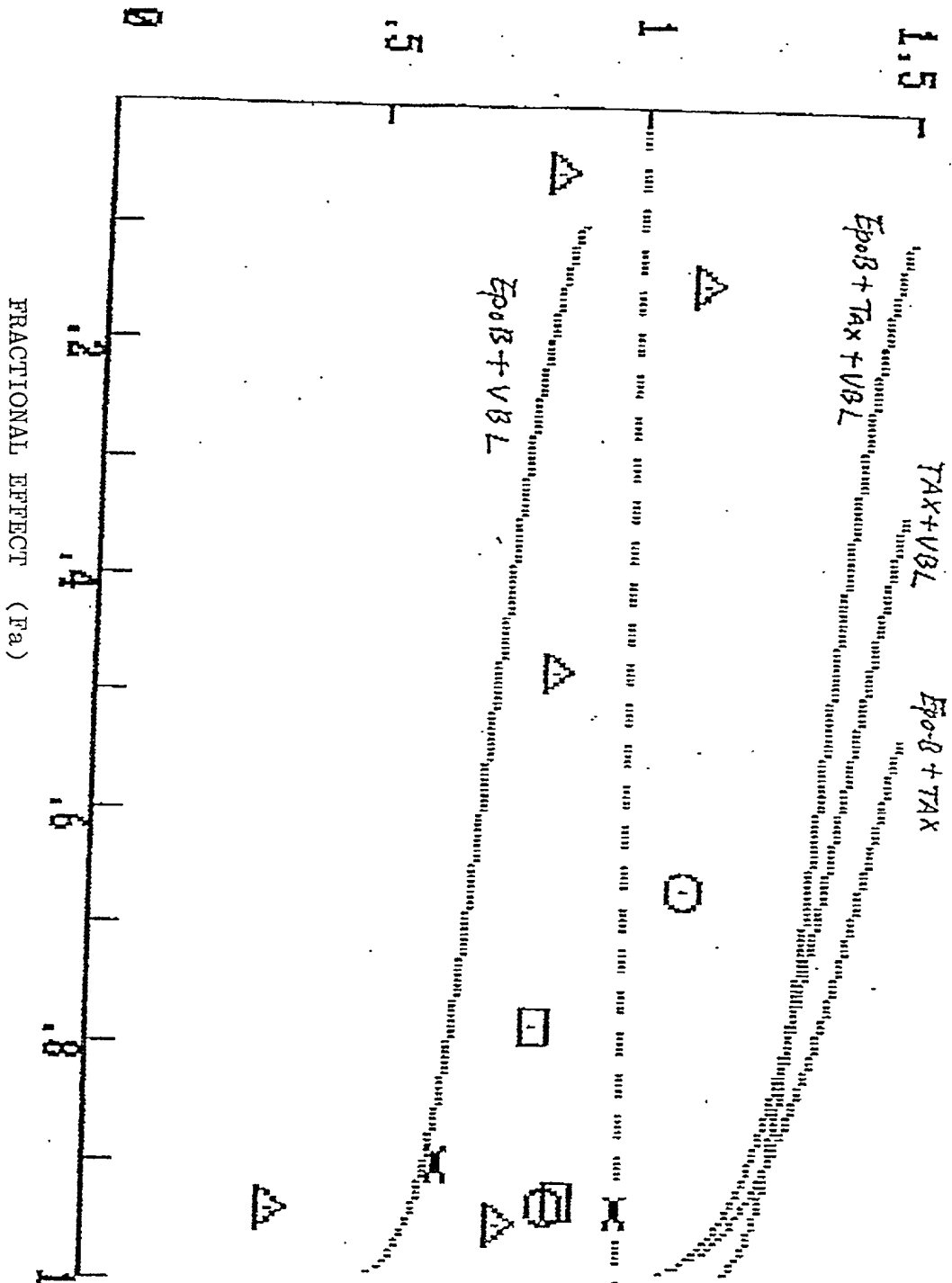
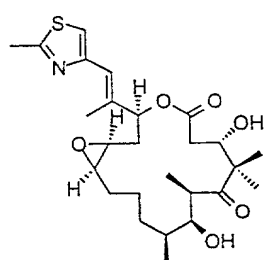
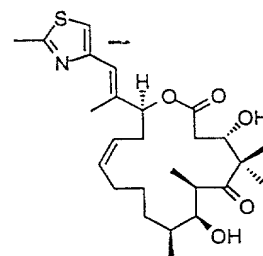


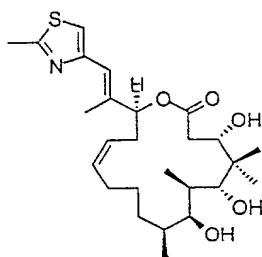
Figure 38



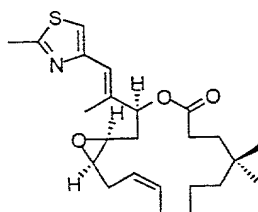
epothilone A
(0.0027)
[0.020]



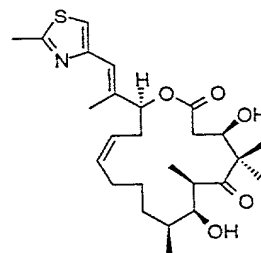
desoxyepothilone A
1
(0.022)
[0.012]



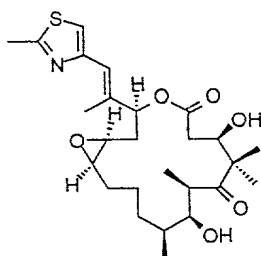
2
(14.23)
[6.28]



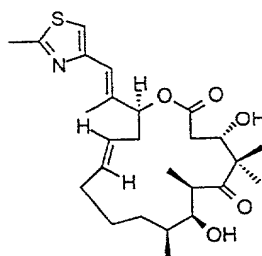
3
(271.1)
[22.4]



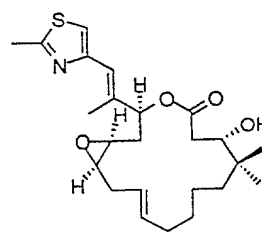
4
(2.12)
[43.0]



5
(>20)
[35.2]

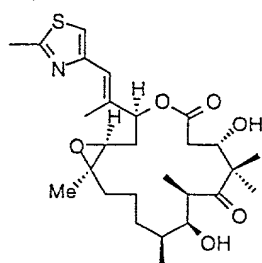


6
(0.052)
[0.035]



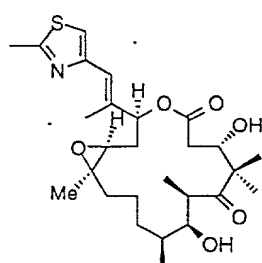
7
(7.36)
[9.82]

Fig. 39



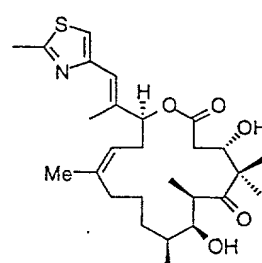
synthetic epothilone B

8
(0.00044)
[0.0026]



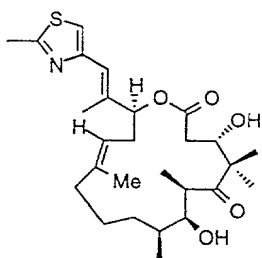
natural epothilone B

9
(0.00017)
[0.0012]

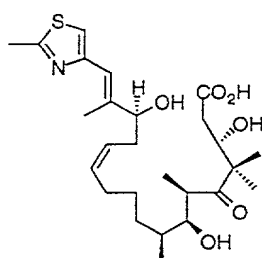


desoxyepothilone B

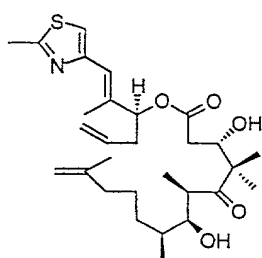
10
(0.0095)
[0.017]



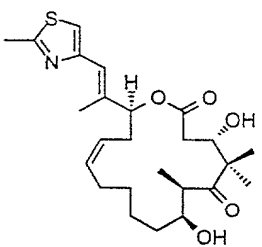
11
(0.090)
[0.262]



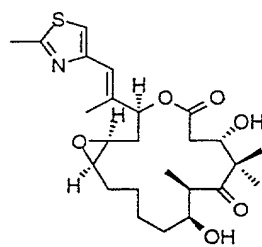
12
(0.79)
[>5]



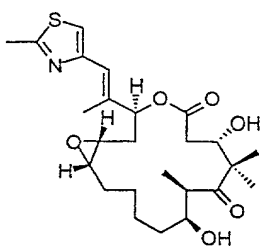
13
(11.53)
[5.63]



14
(5.42)
[5.75]

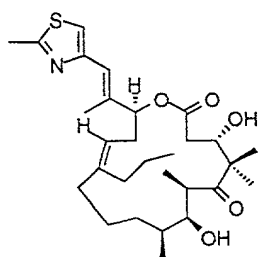


15
(0.96)
[5.95]

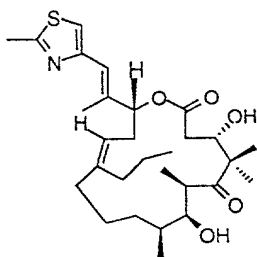


16
(7.47)
[16.48]

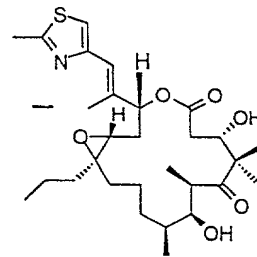
Fig. 40



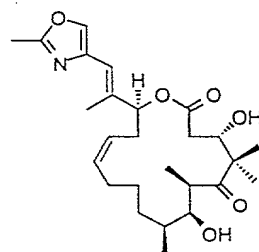
17
(0.090)
[0.254]



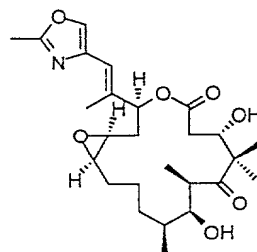
18
(1158)
[>720]



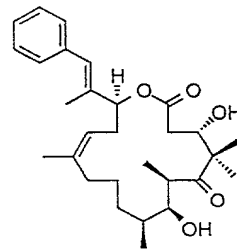
19
(0.96)
[>1.0]



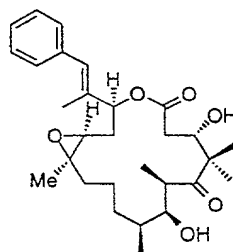
20
(0.030)
[0.049]



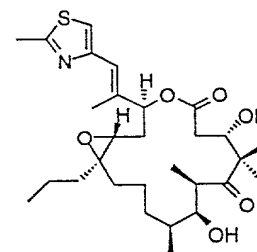
21



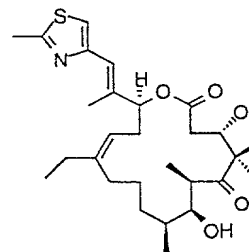
22
(0.098)
[0.146]



23

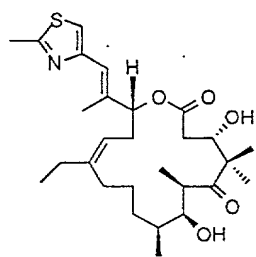


24
(0.0043)
[0.0321]

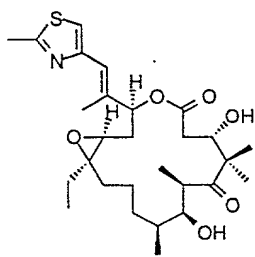


25
(0.021)
[0.0771]

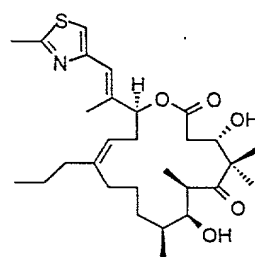
Fig. 41



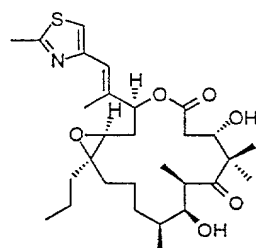
26
(0.055)
[0.197]



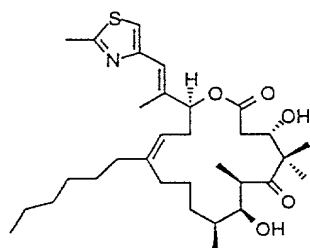
27
(0.0010)
[0.0072]



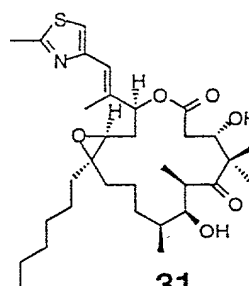
28
(0.039)
[0.067]



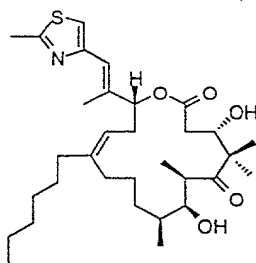
29
(0.0038)
[0.0064]



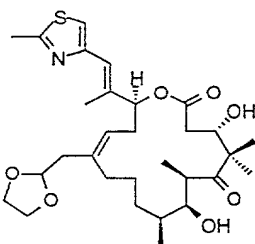
30
(0.044)
[0.108]



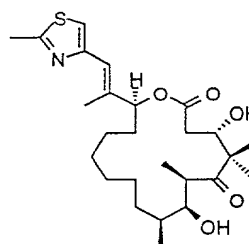
31
(0.027)
[0.049]



32
(0.063)
[0.380]

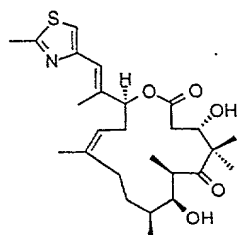


33
(0.0031)
[0.0093]

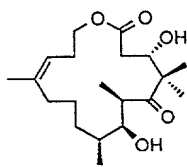


34
(0.143)
[0.276]

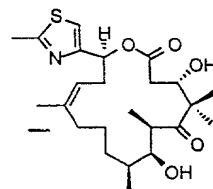
Fig. 42(A)



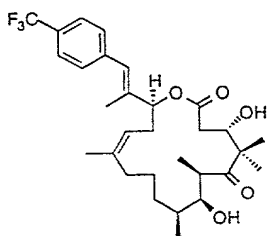
35
(>10)
[8.95]



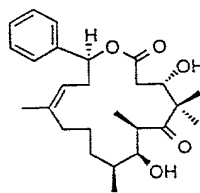
36
(234.5)
[>10]



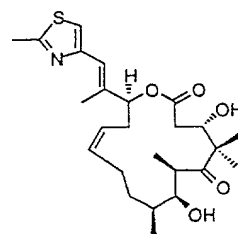
37
(3.25)
[1.20]



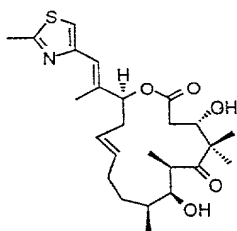
38
(0.254)
[>5.0]



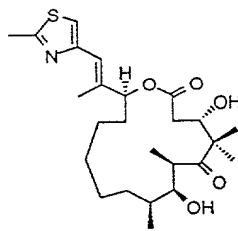
39
(1.80)
[>5.0]



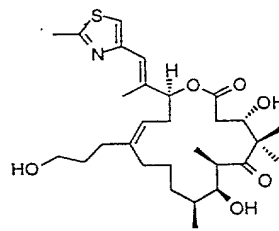
40
(36.9)
[47.3]



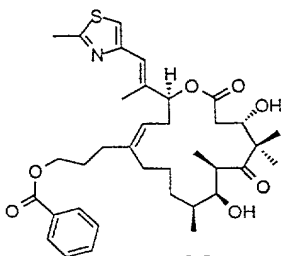
41
(60.1)
[59.2]



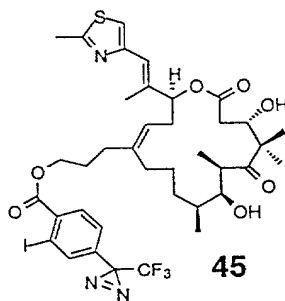
42
(7.41)
[12.9]



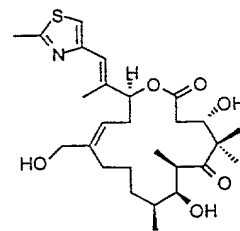
43
(0.0095)
[0.167]



44 (0.250)
[0.905]

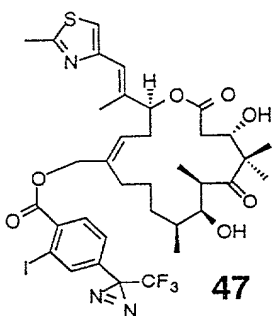


45

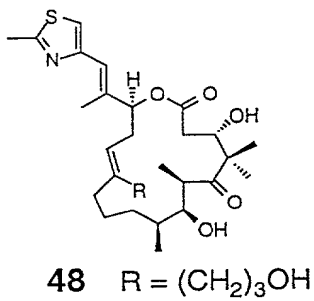


46 (0.049)
[>1.0]

Fig. 42(B)

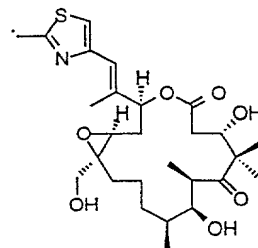


47



48

$\text{R} = (\text{CH}_2)_3\text{OH}$



49

Fig. 42(C)

Fig. 43(A)

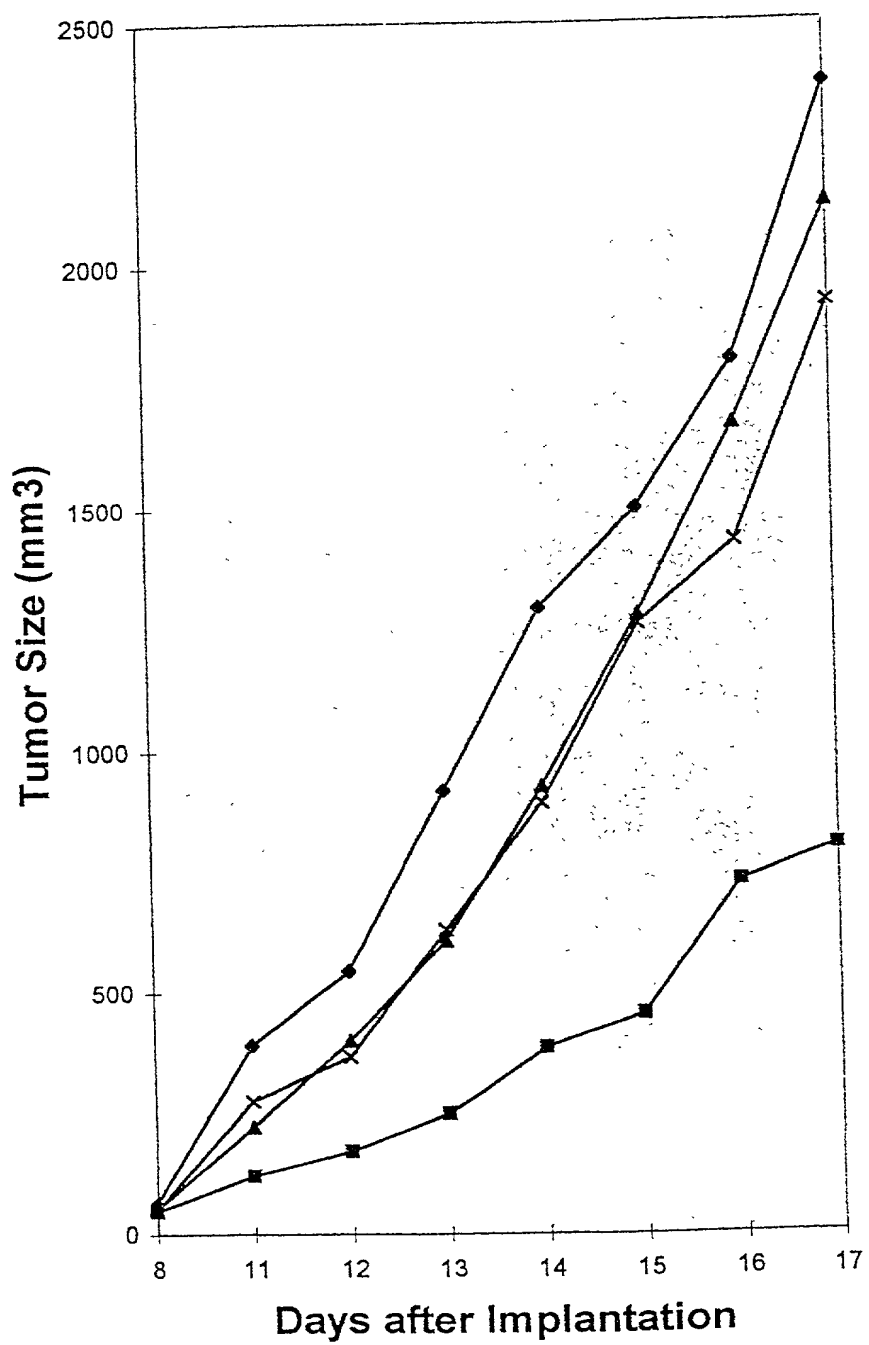
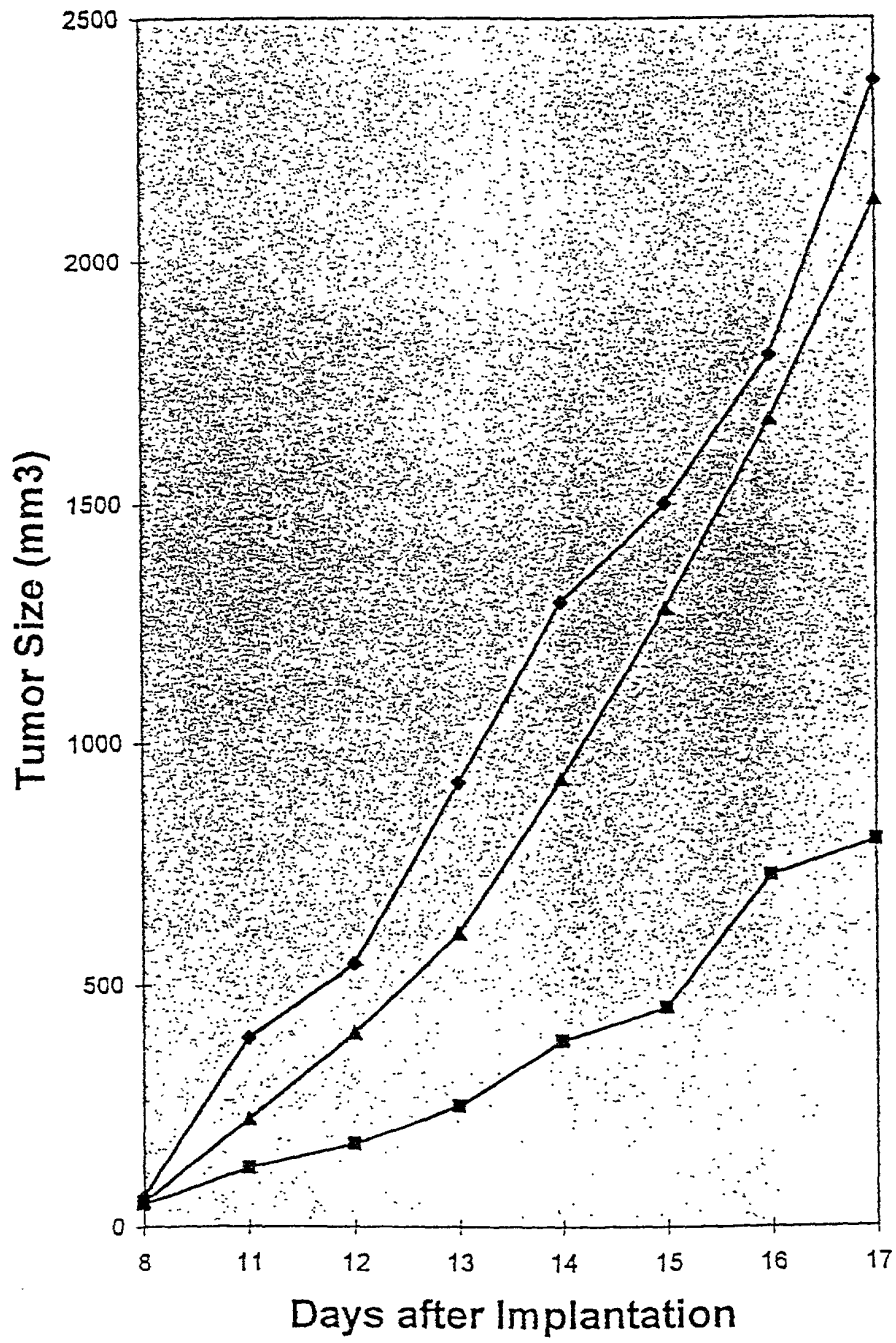


Fig. 43(B)



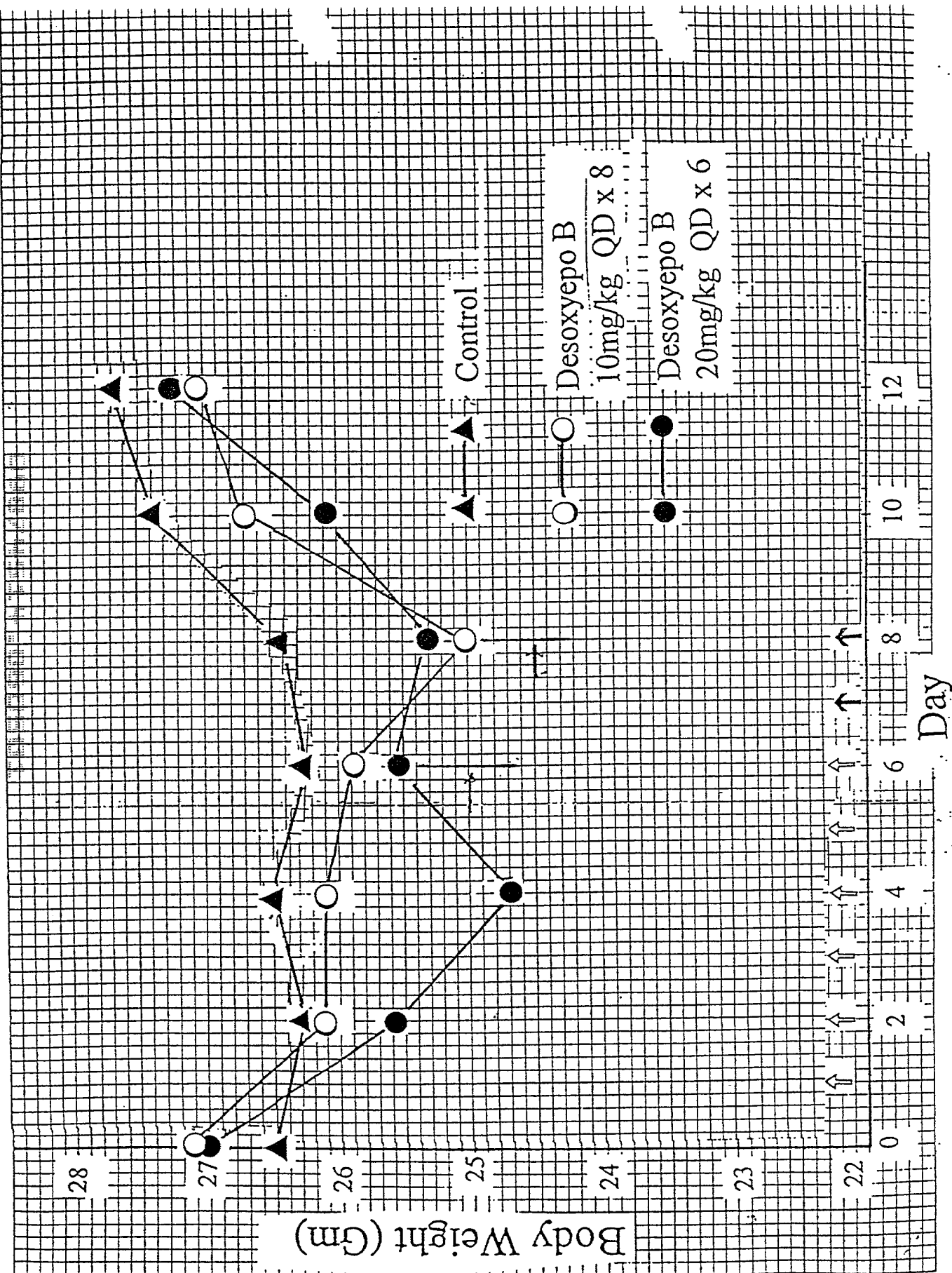


Fig. 44(A)

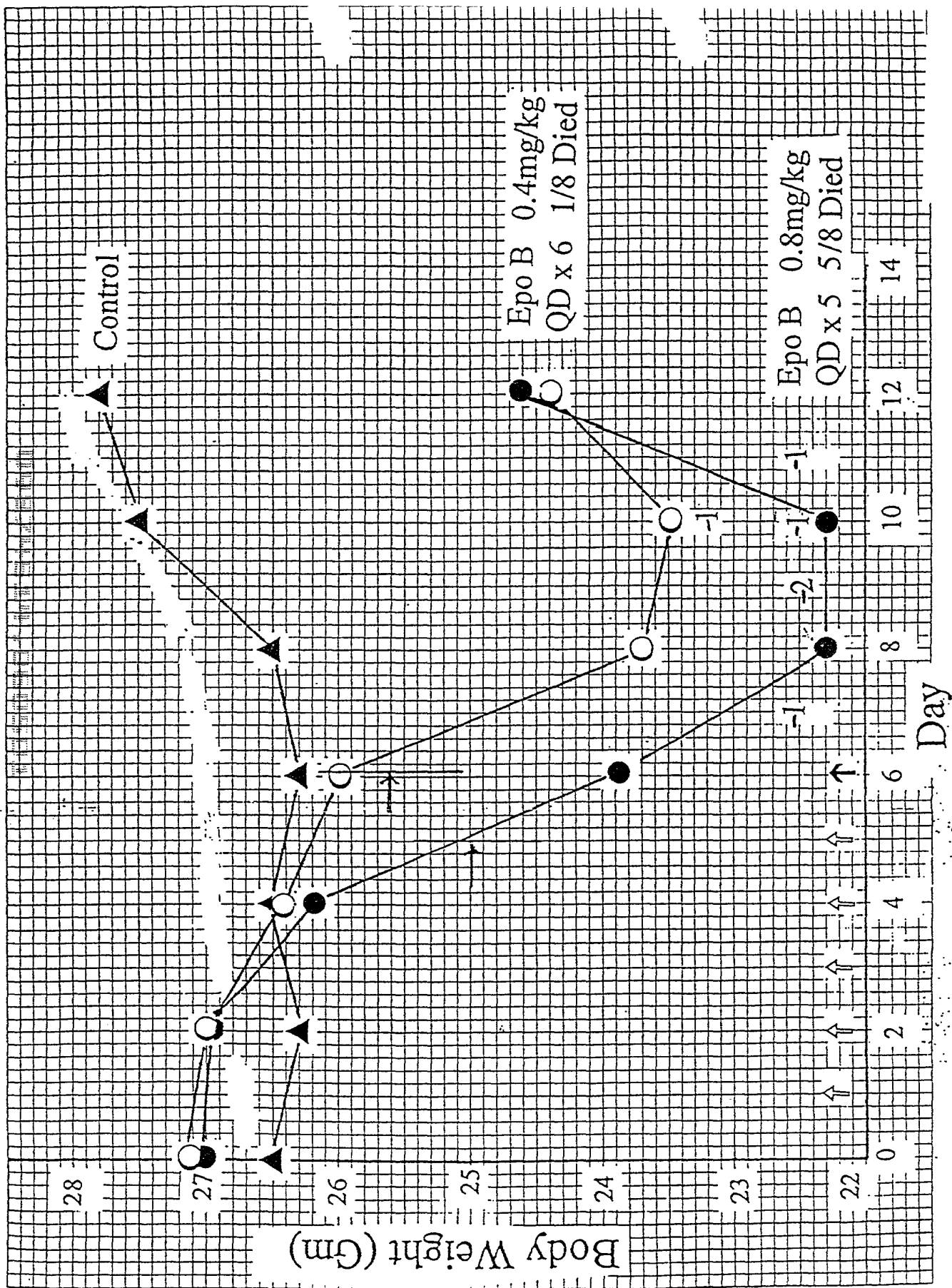


Fig. 44(B)

Fig. 45(A)

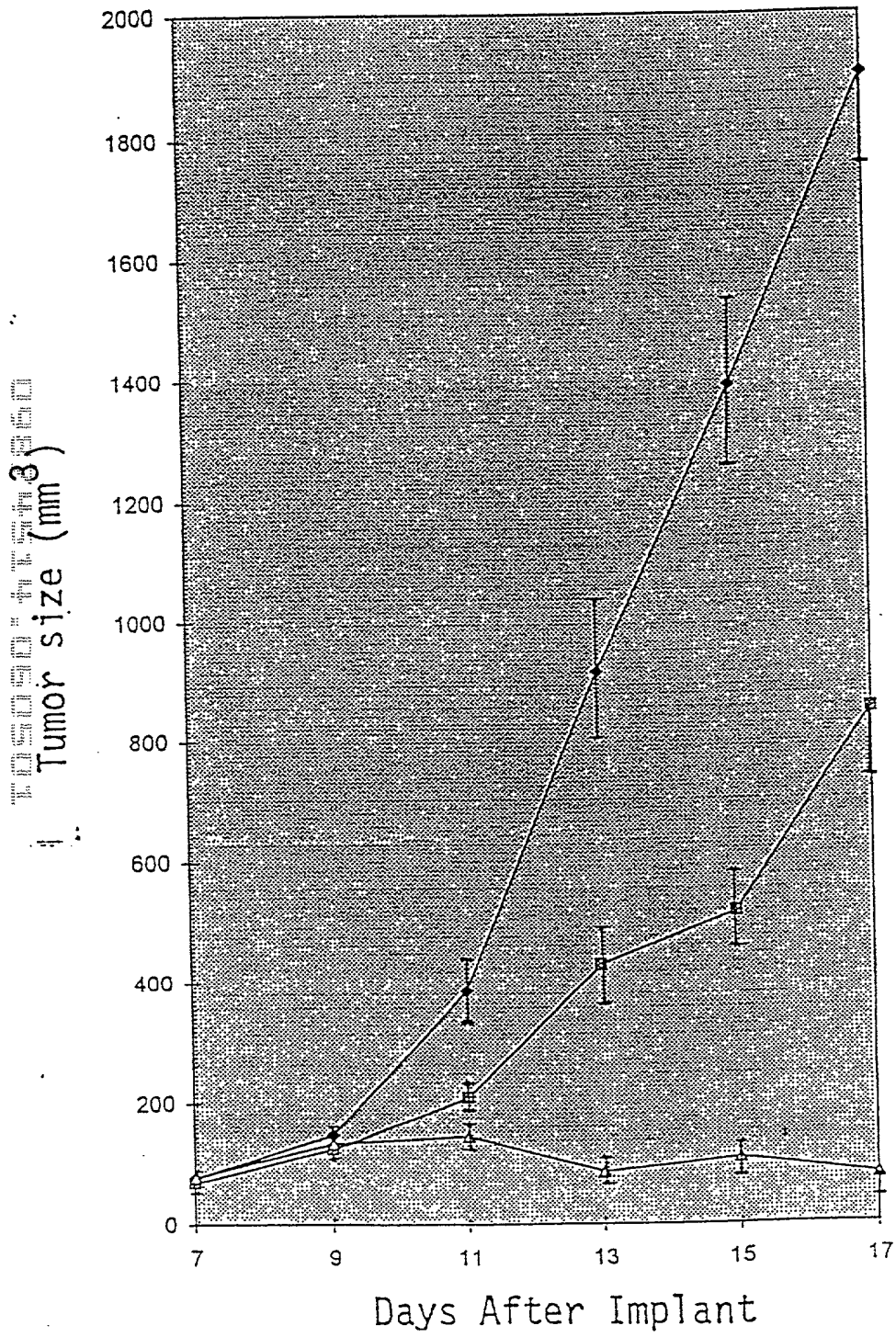
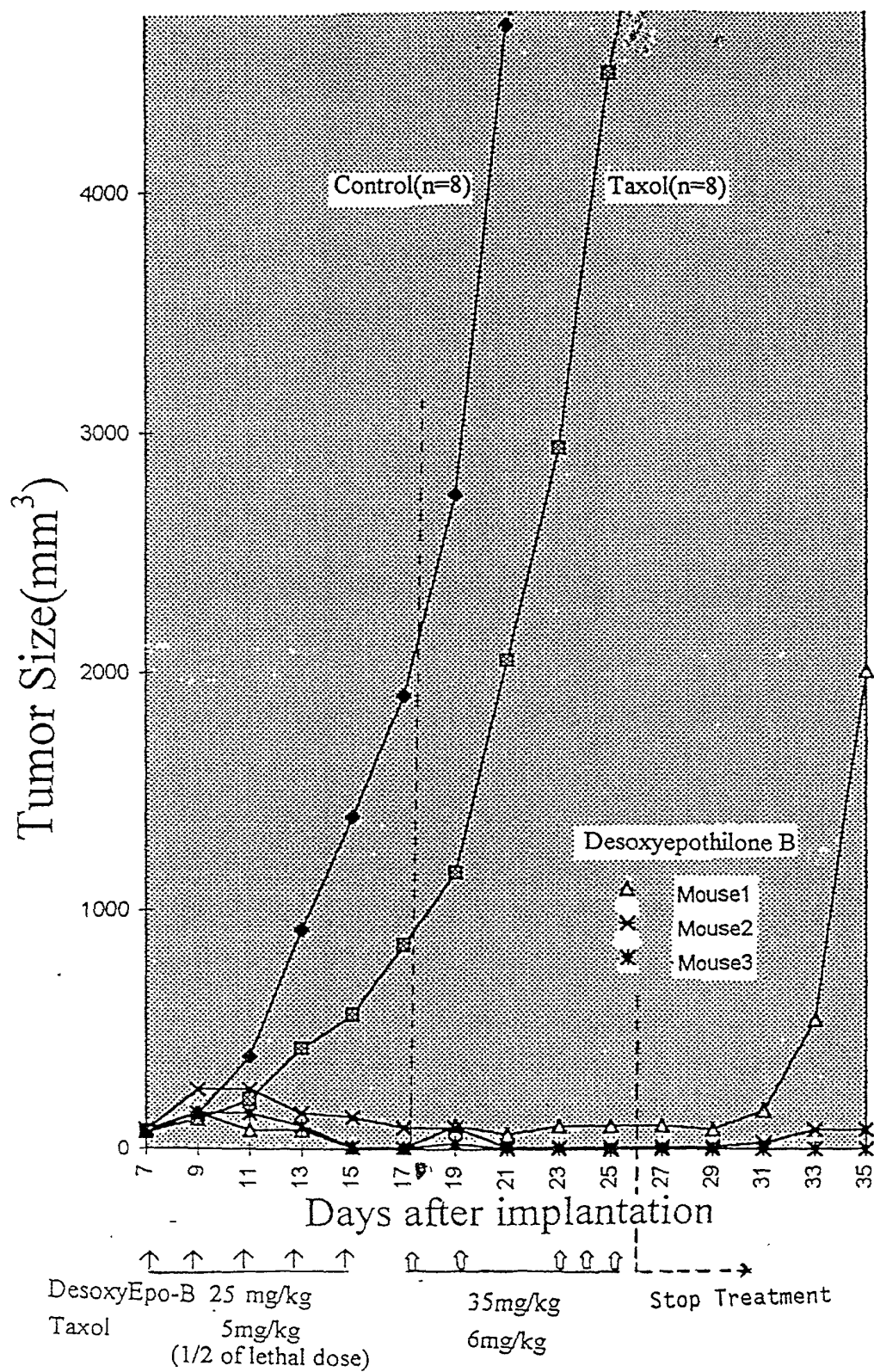


Fig. 45(B)



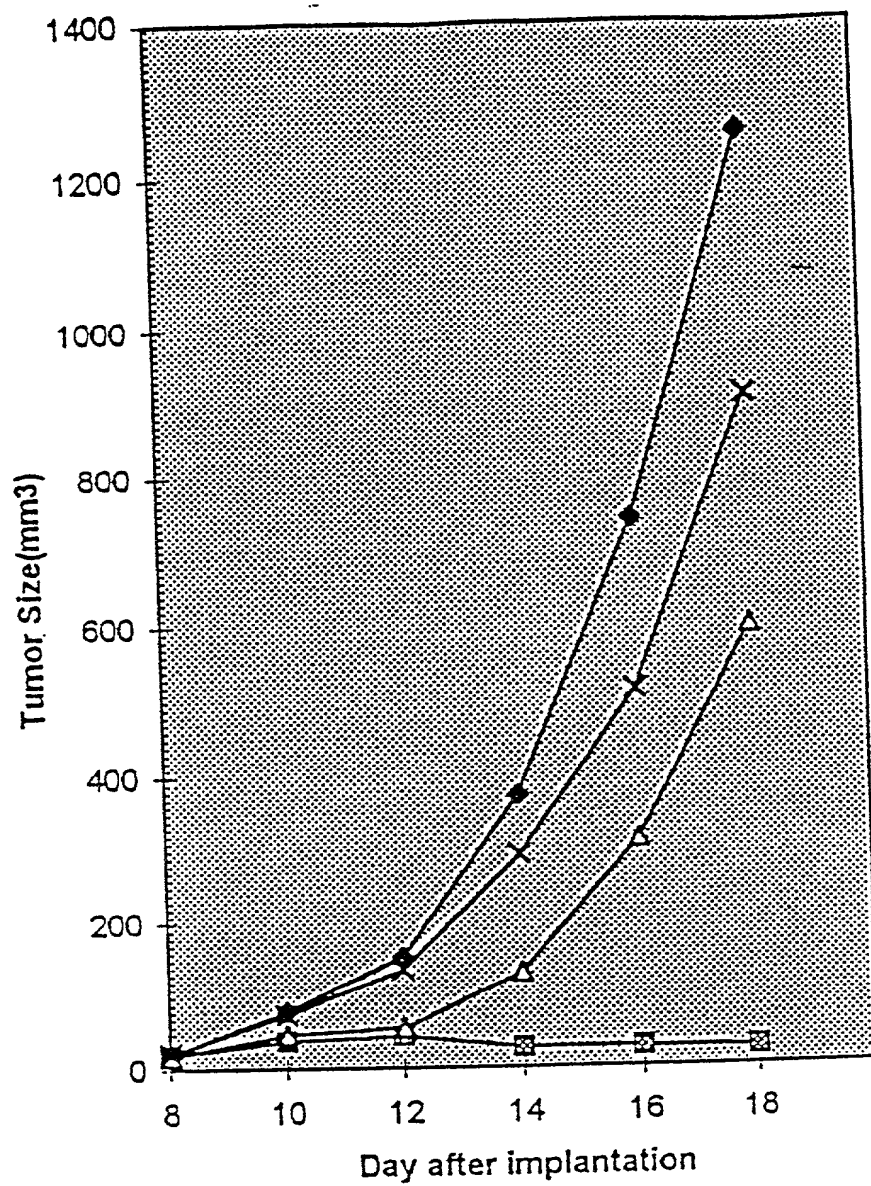
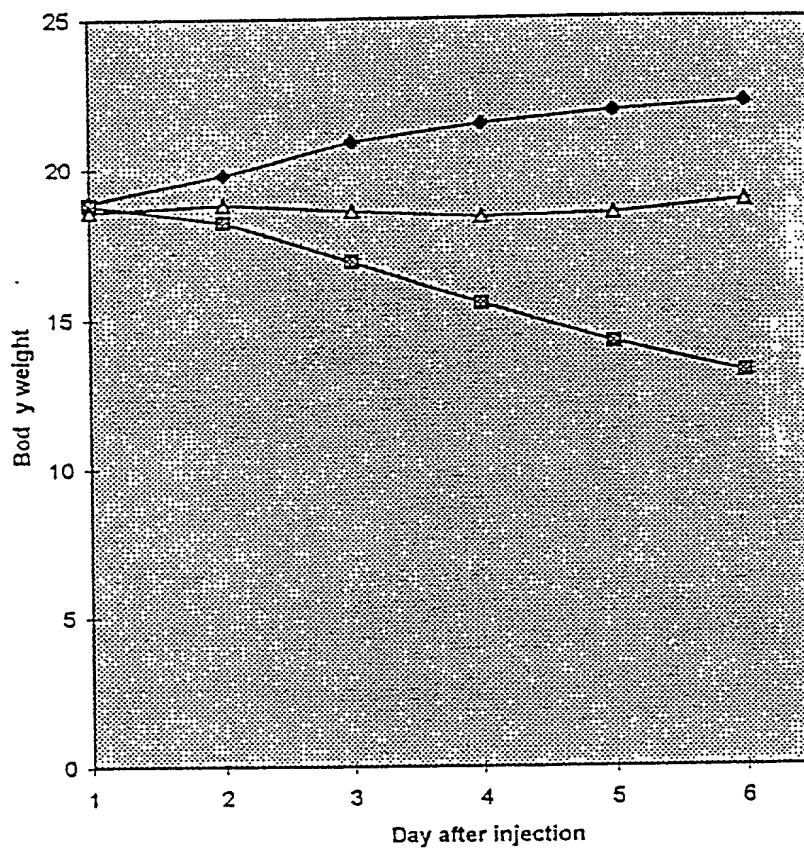


Fig. 46

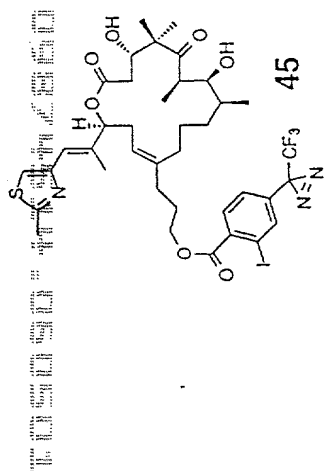
Fig. 47



The chemical structure of compound 1 is a complex macrocycle. It features a thiazole ring substituted with a methyl group and a long chain that forms the macrocycle. The chain includes several hydroxyl groups and a ketone group. The stereochemistry is indicated with wedges and dashes.

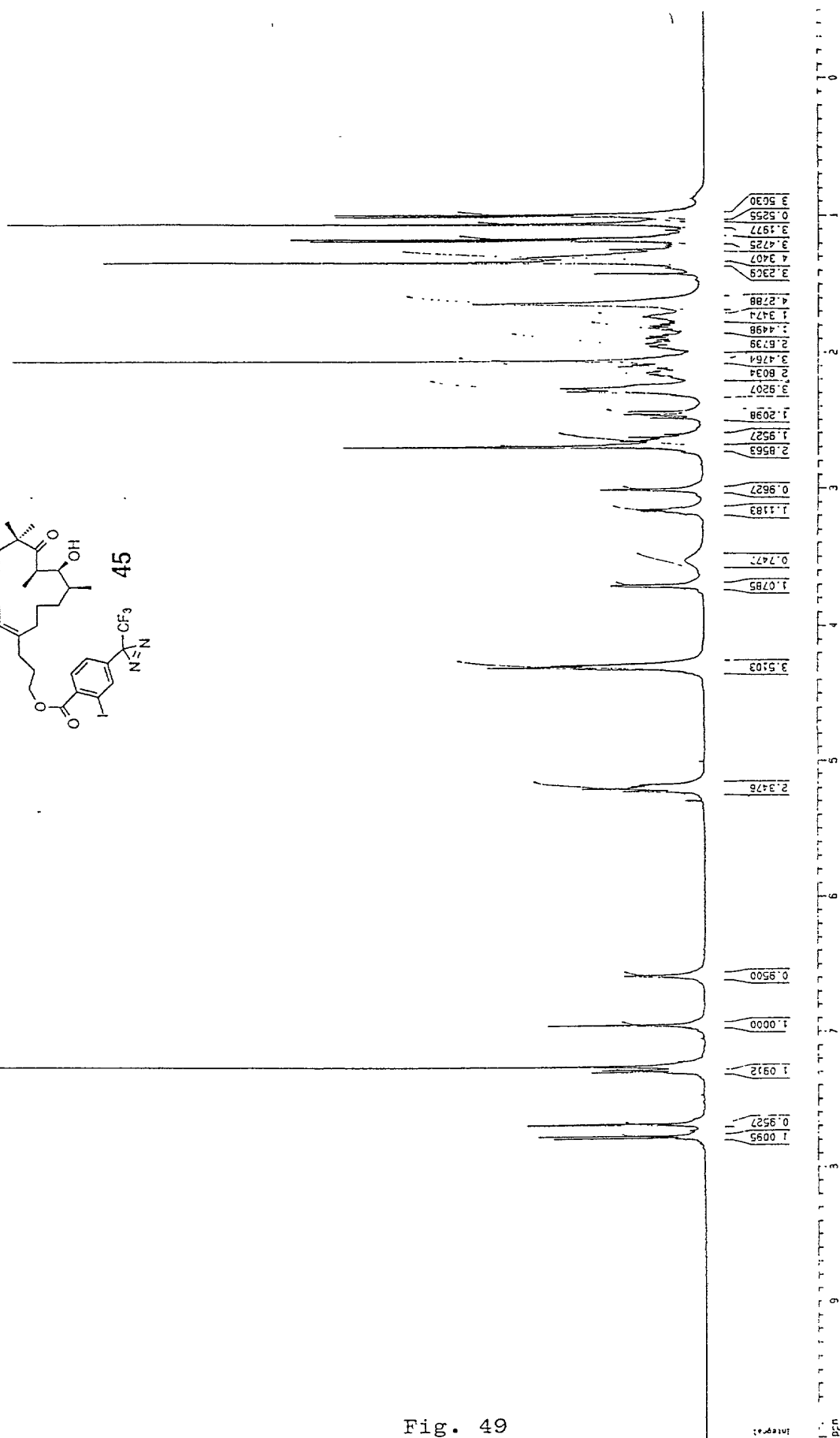
Fig. 48

Fig. 48



500 MHz, CDCl₃, rt.

Fig. 49



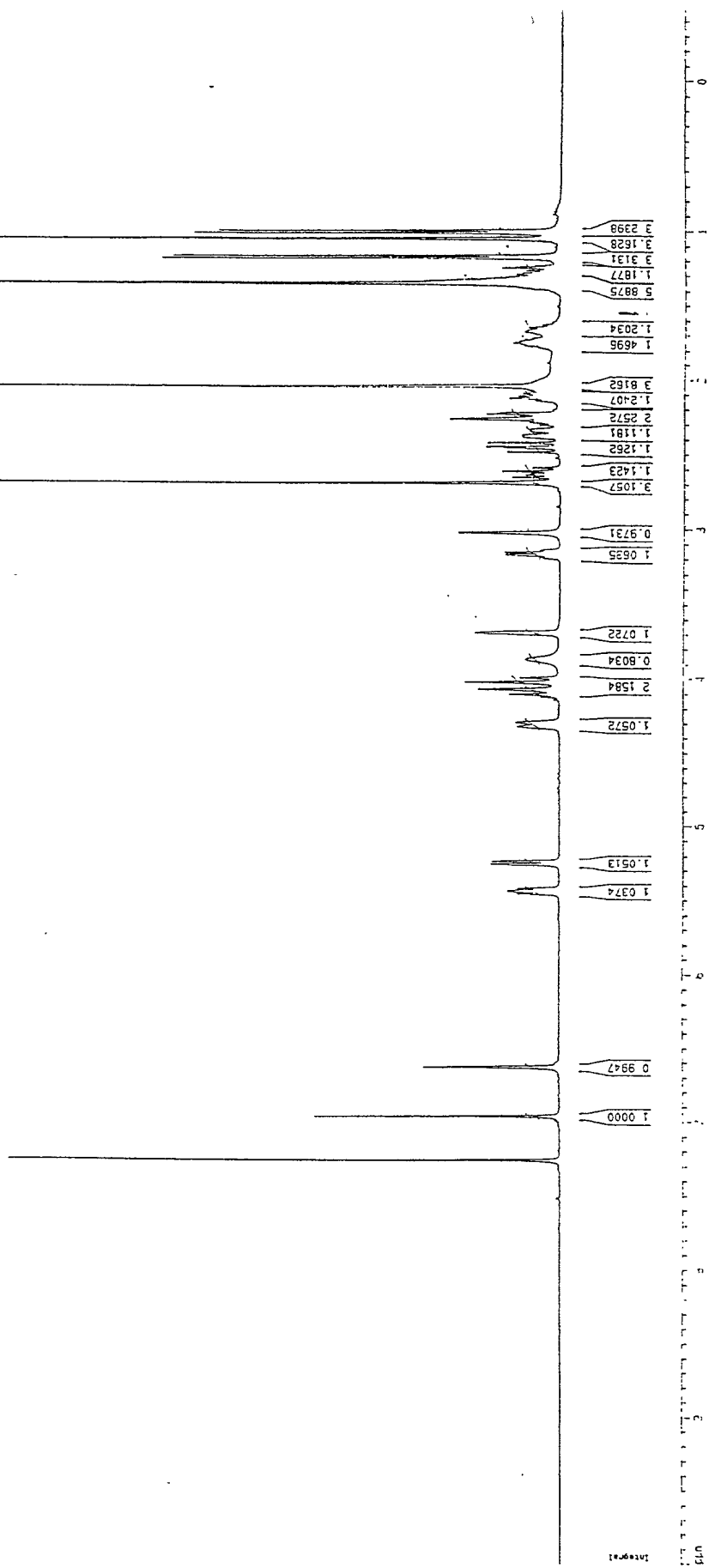
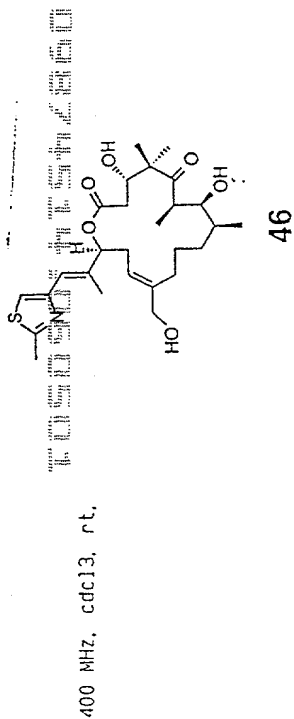


Fig. 50

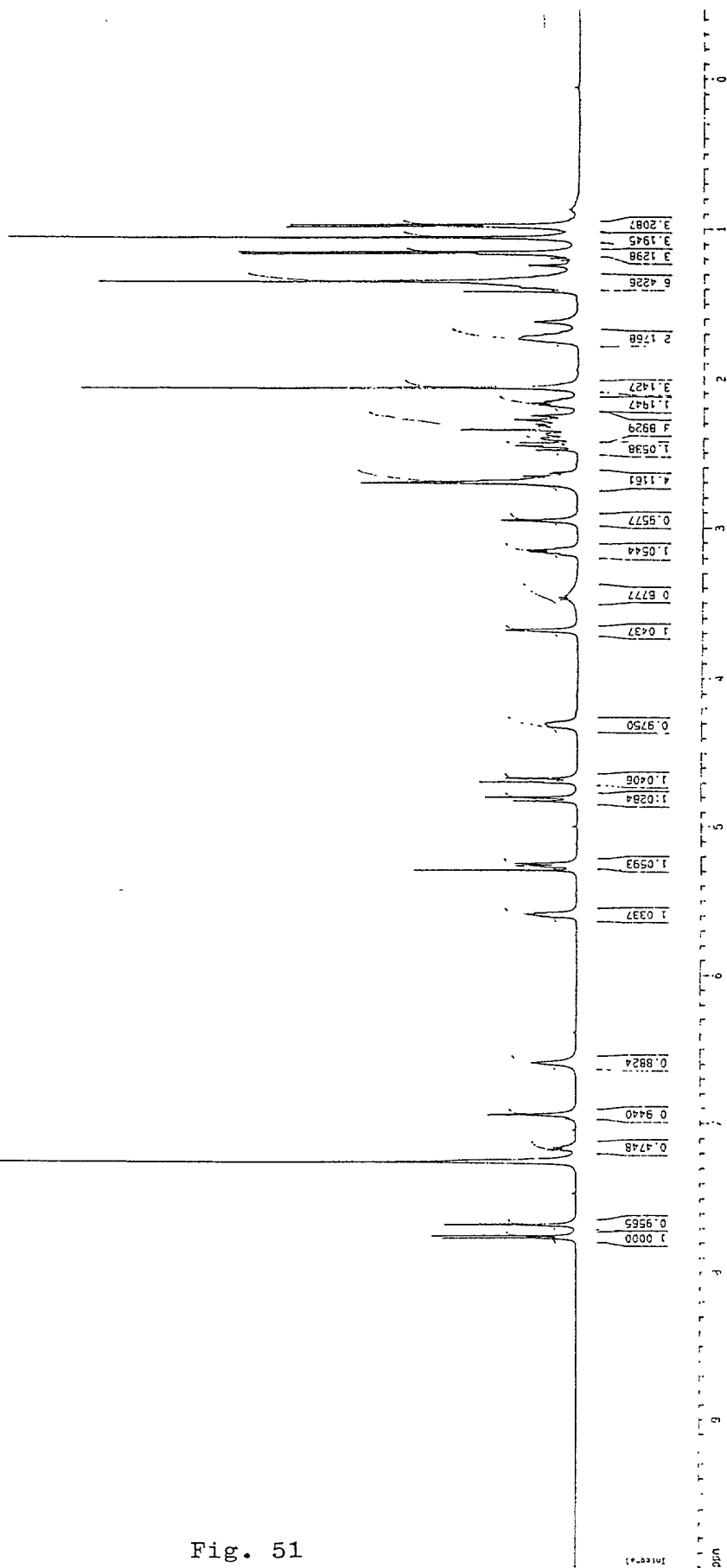
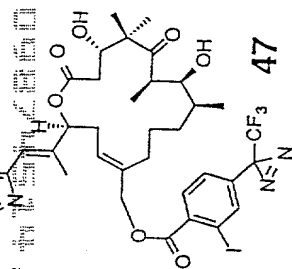


Fig. 51

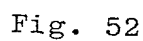


FIG. 1A

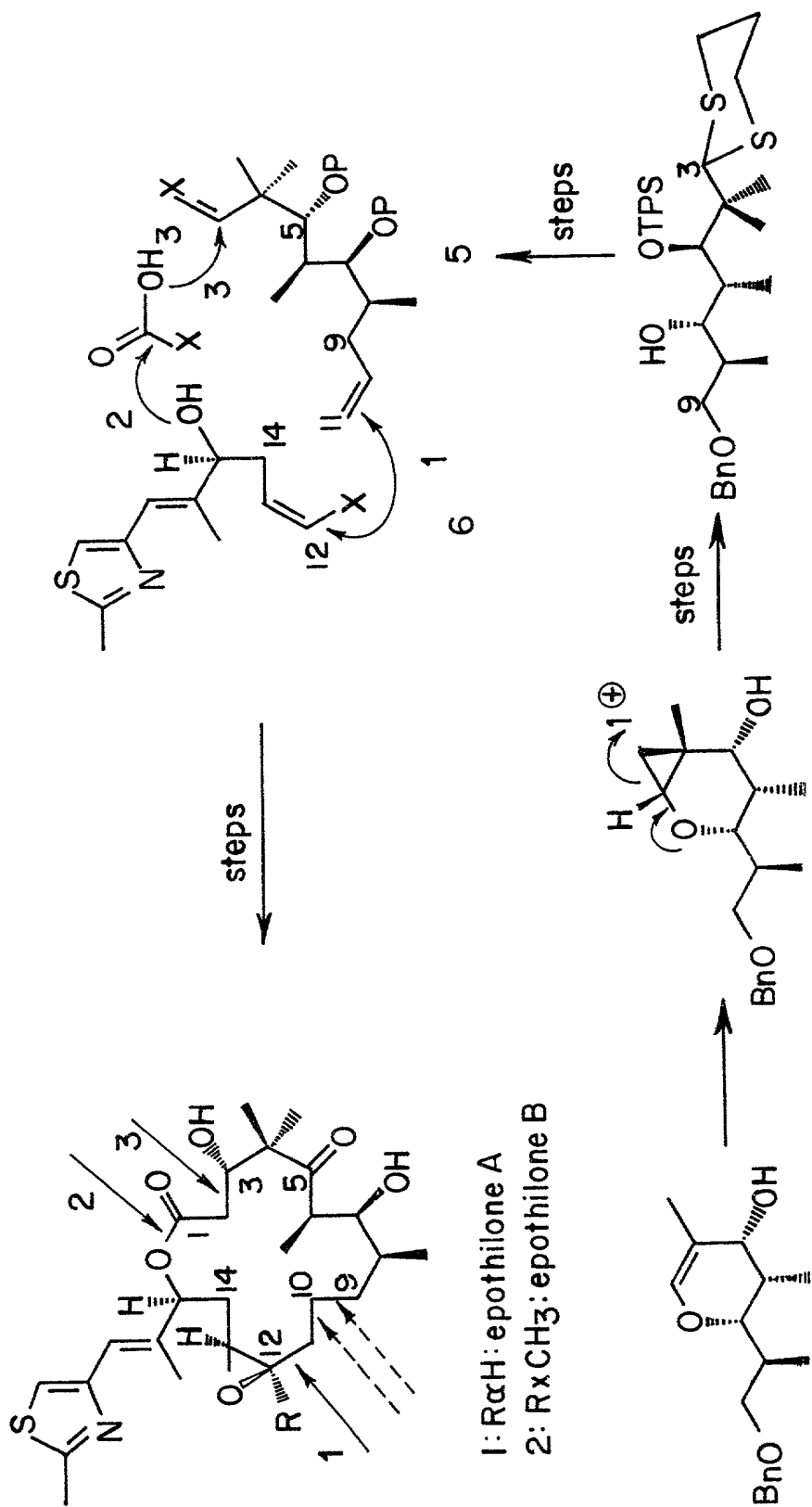


FIG. 1B

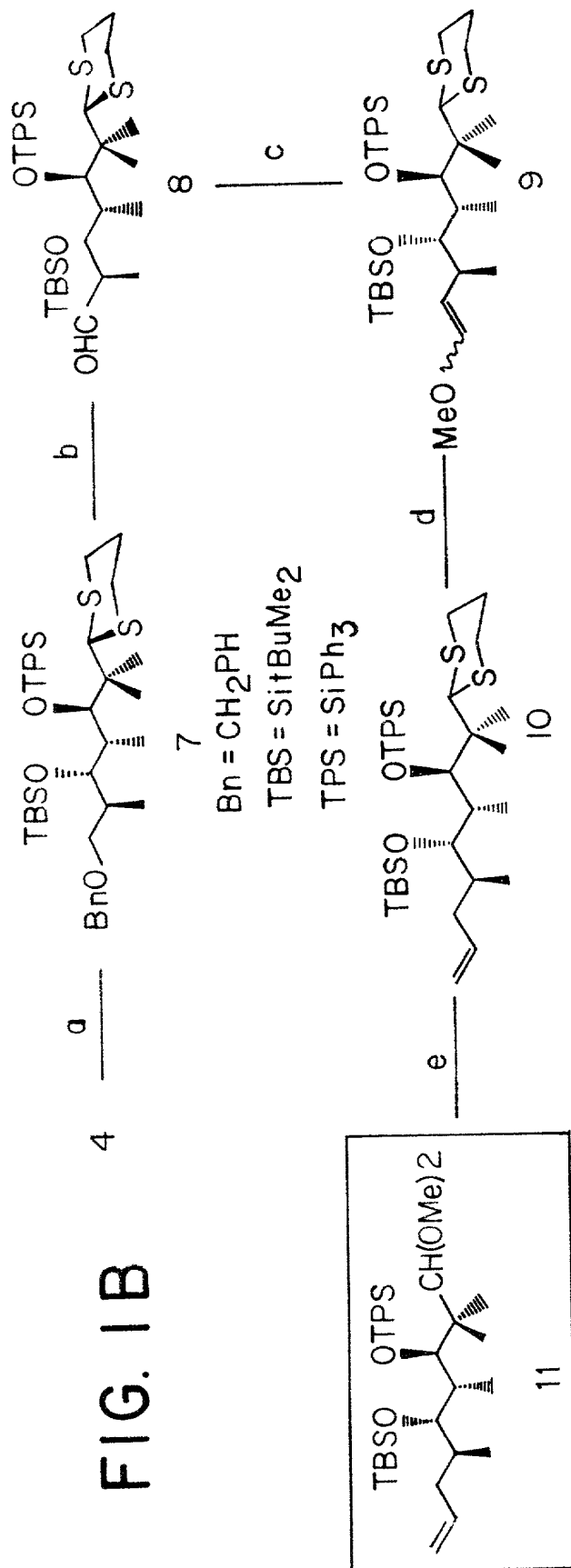
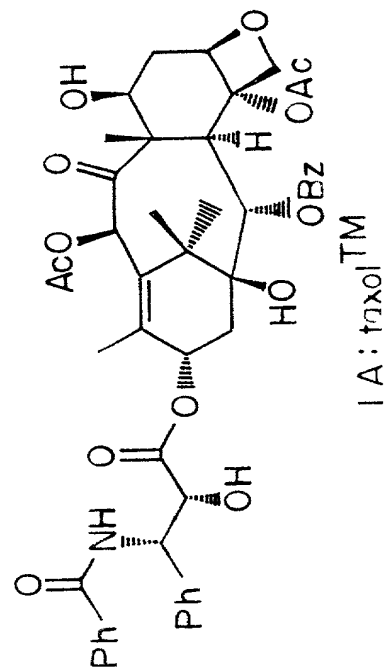
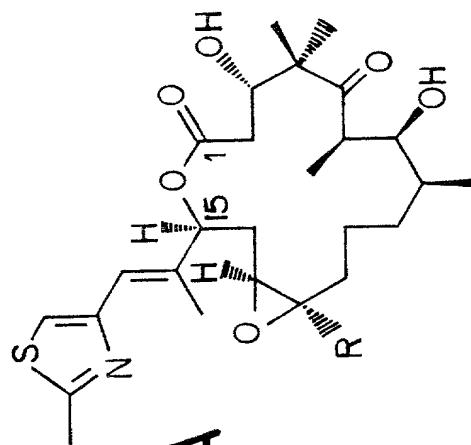


FIG. 12B



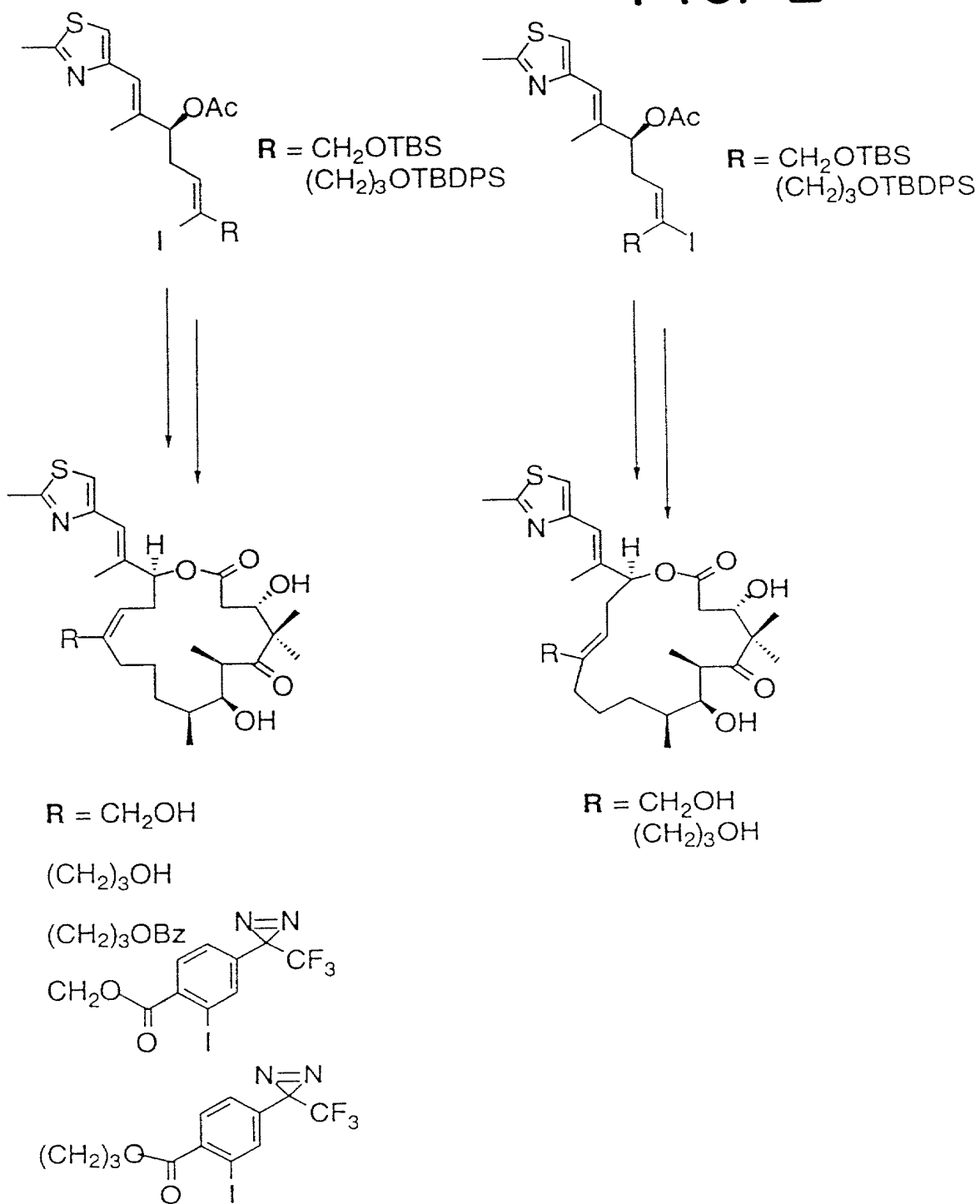
1A: trioxolTM B

FIG. 12A



R= H: epothilone A
R= CH₃: epothilone B

FIG. 2



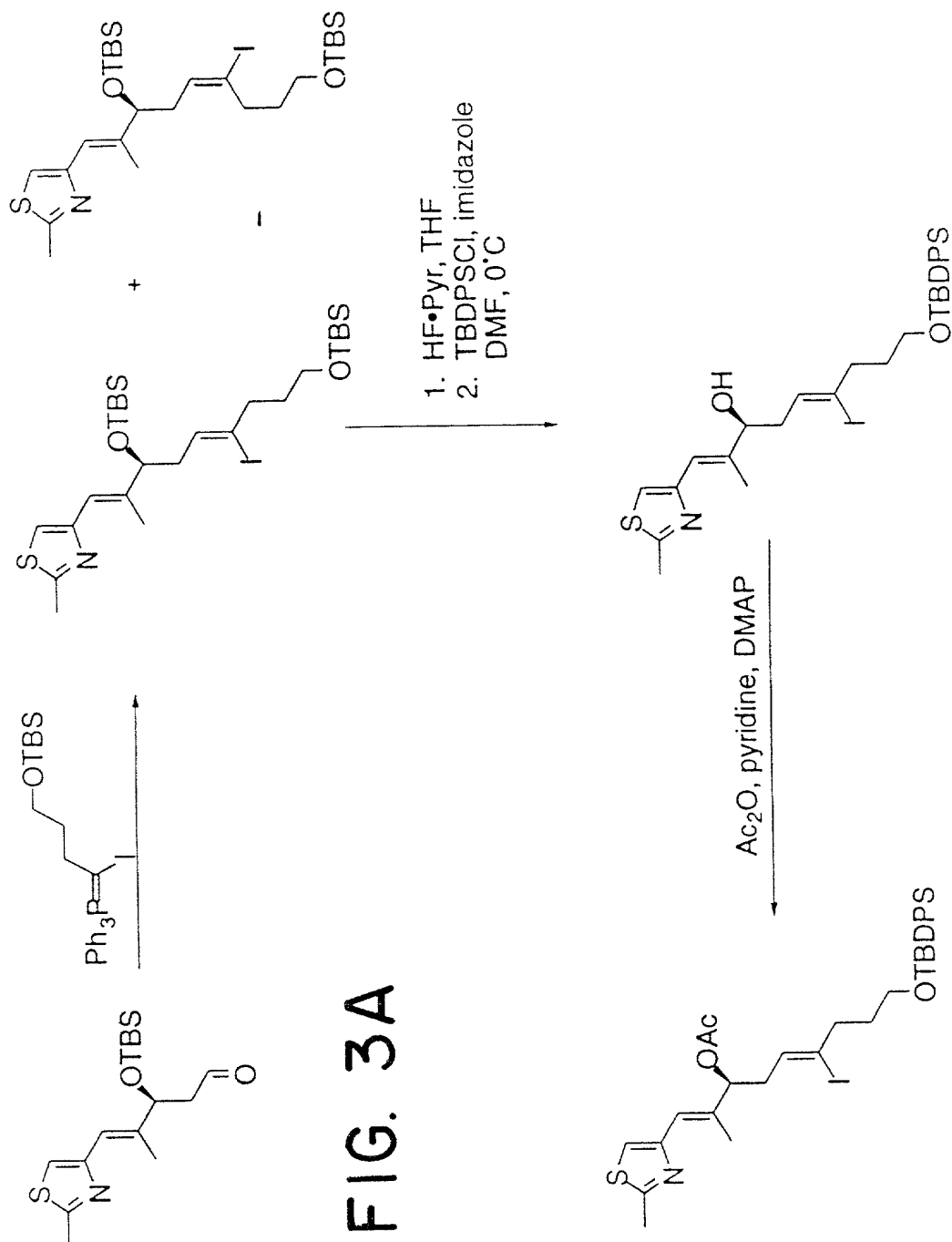


FIG. 3A

FIG. 3B

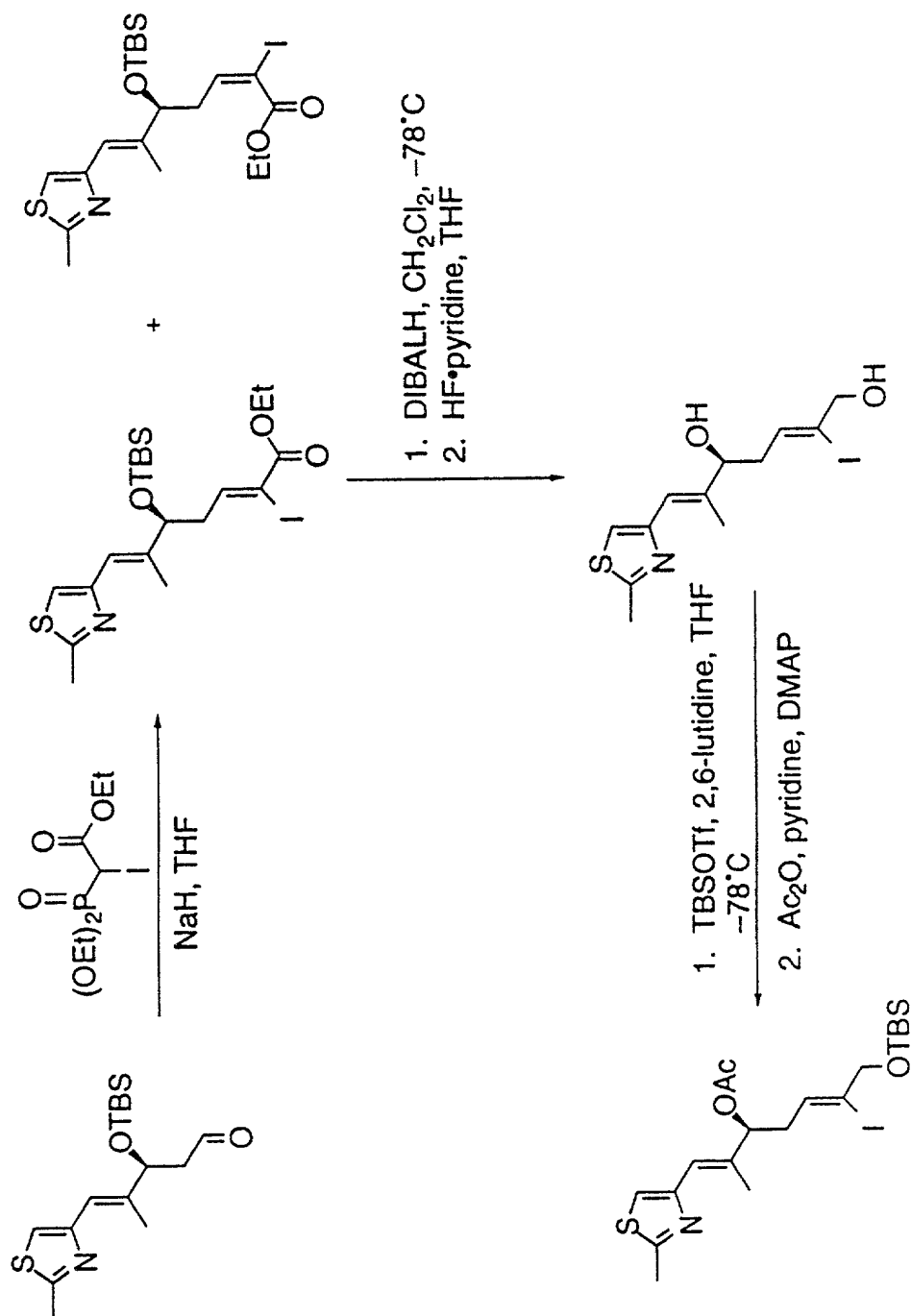
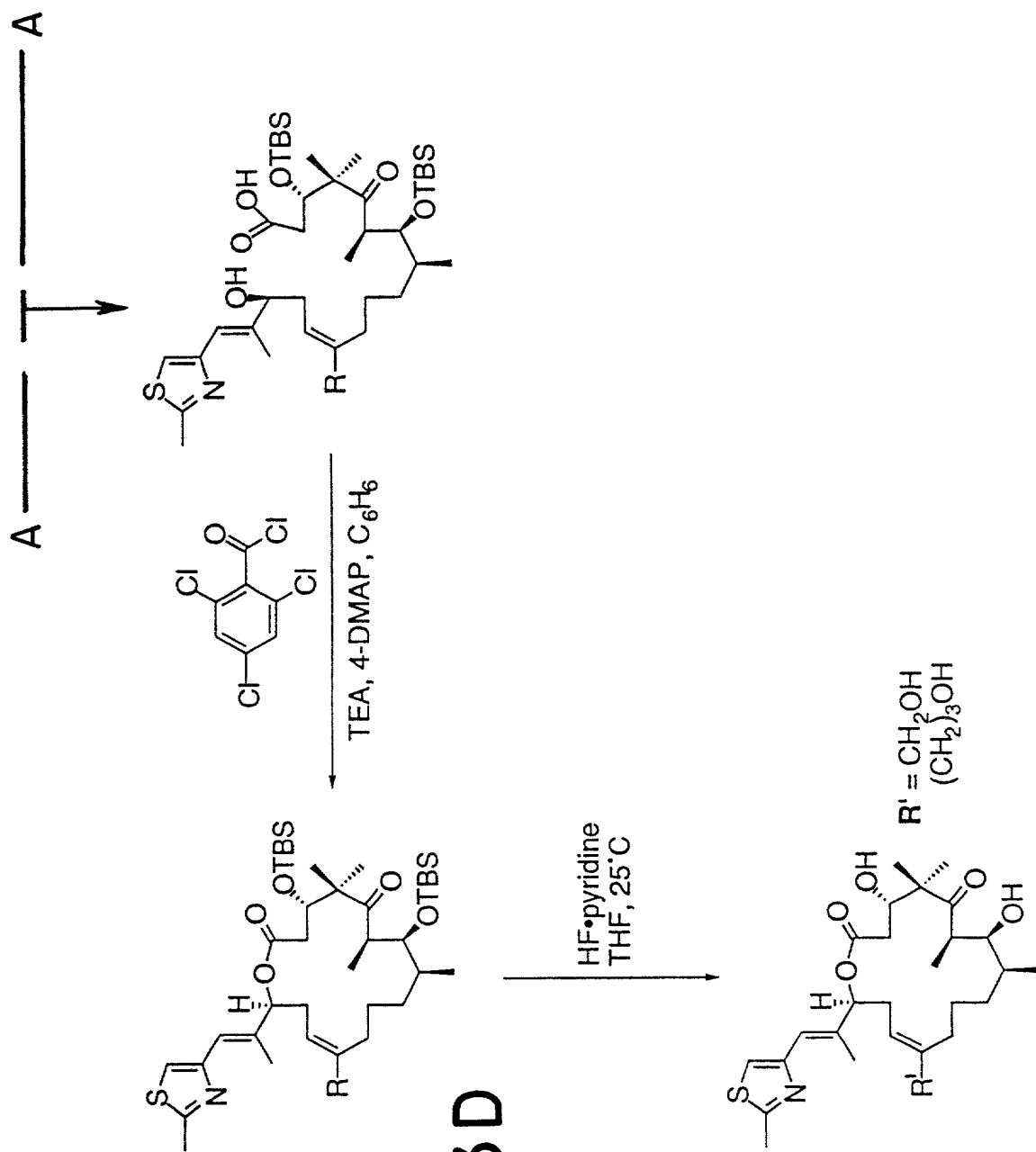


FIG. 3C





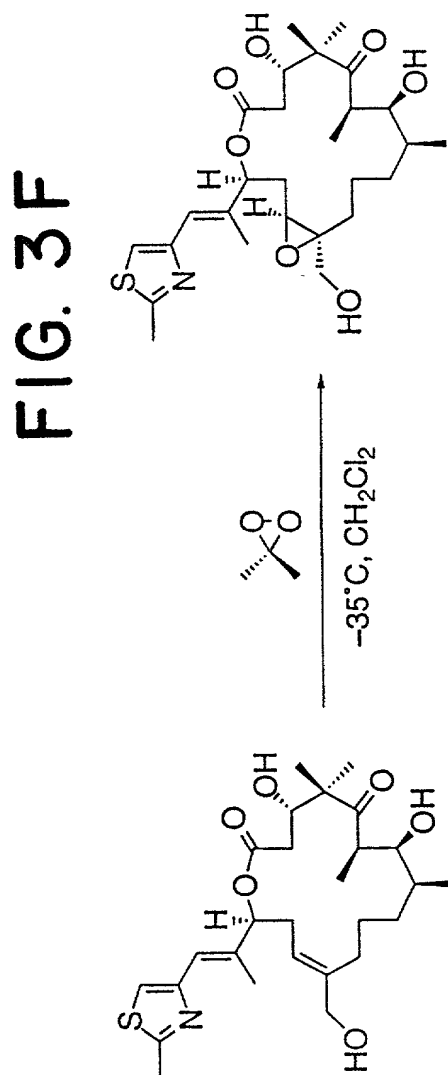
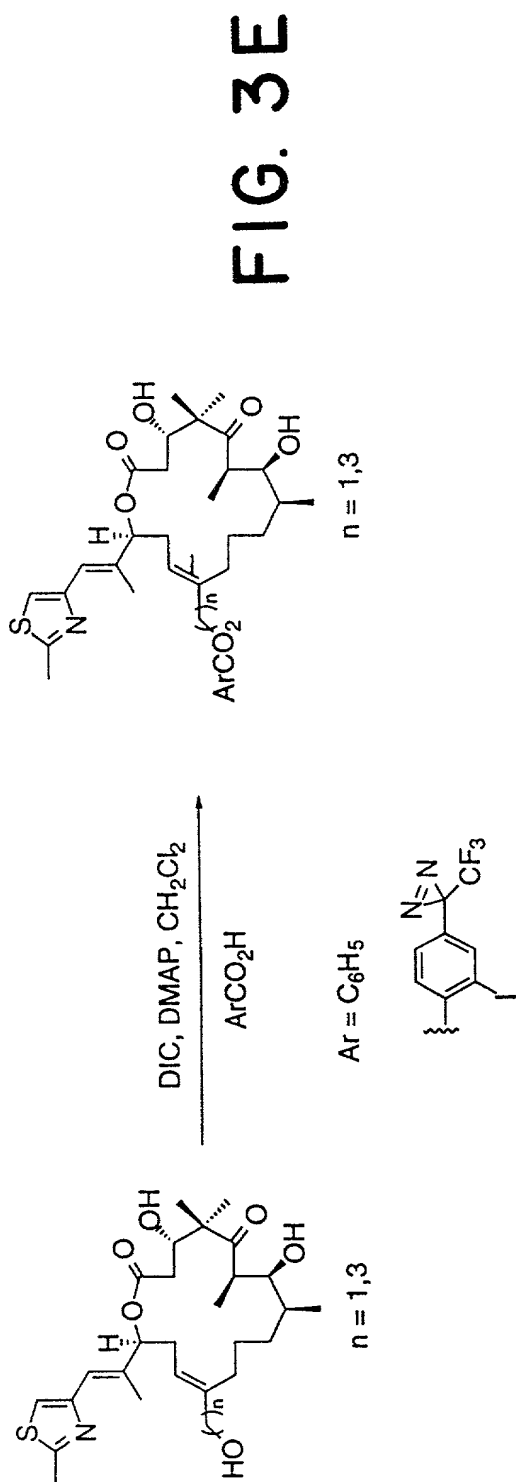


FIG. 4A

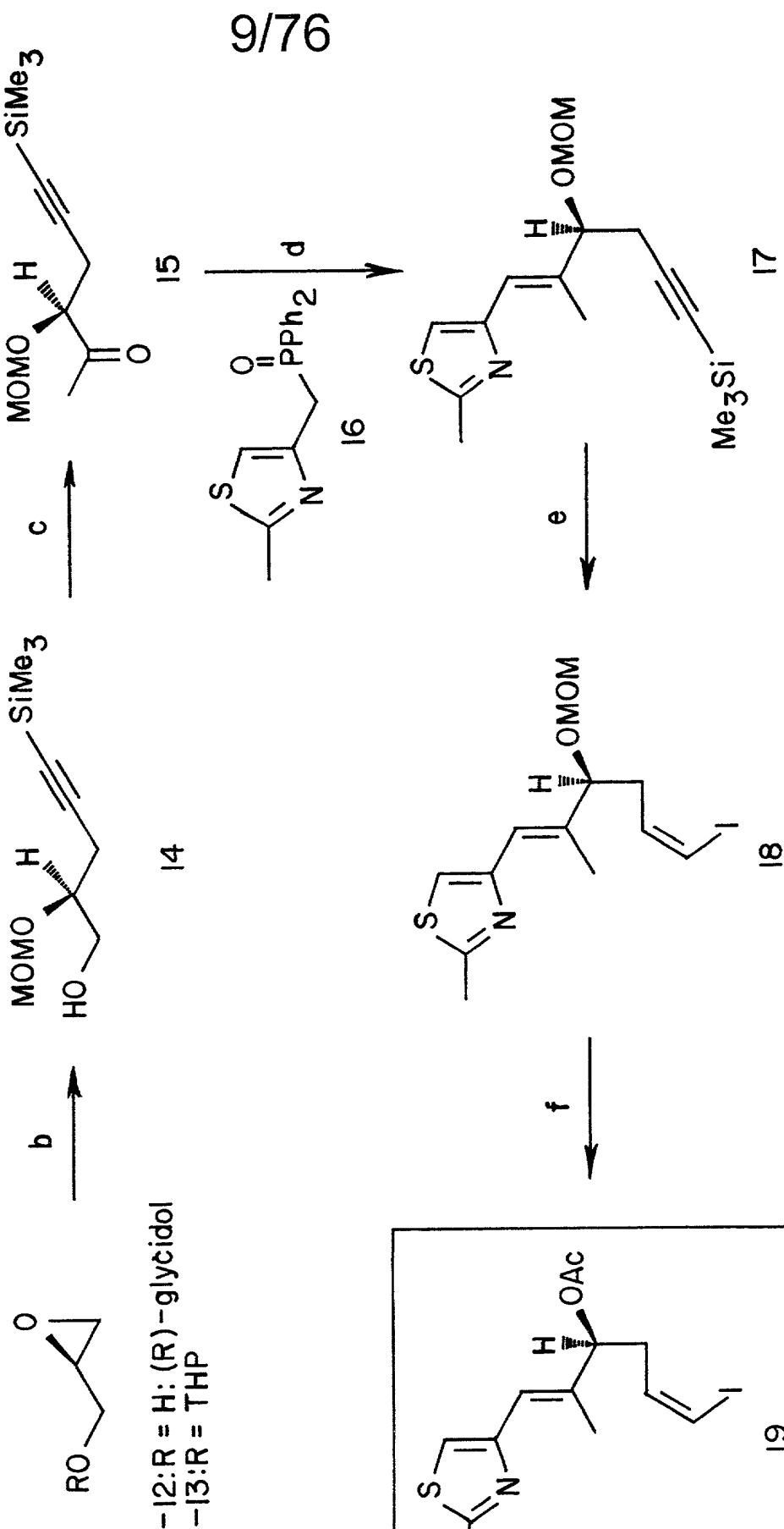


FIG. 4B

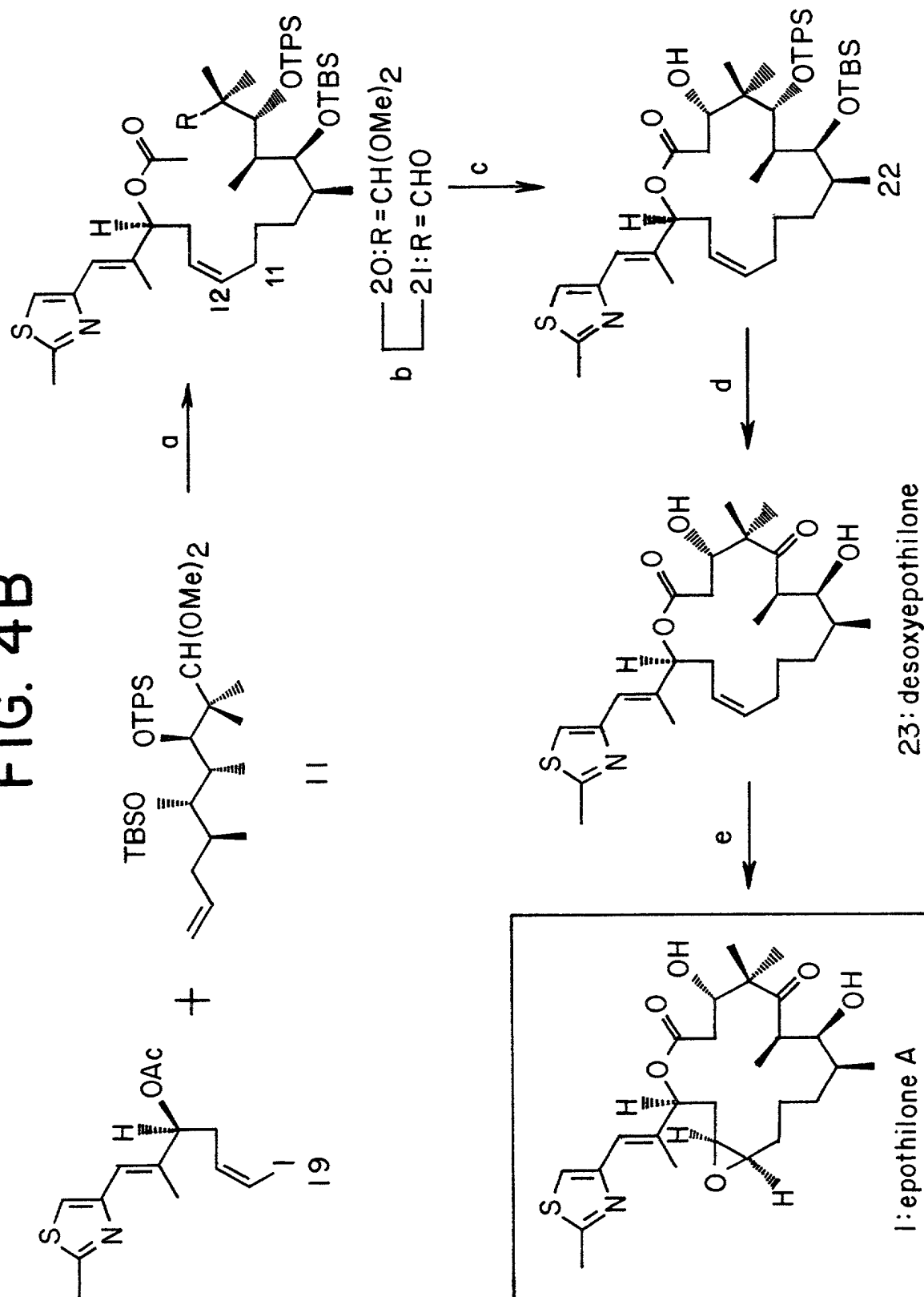


FIG. 5

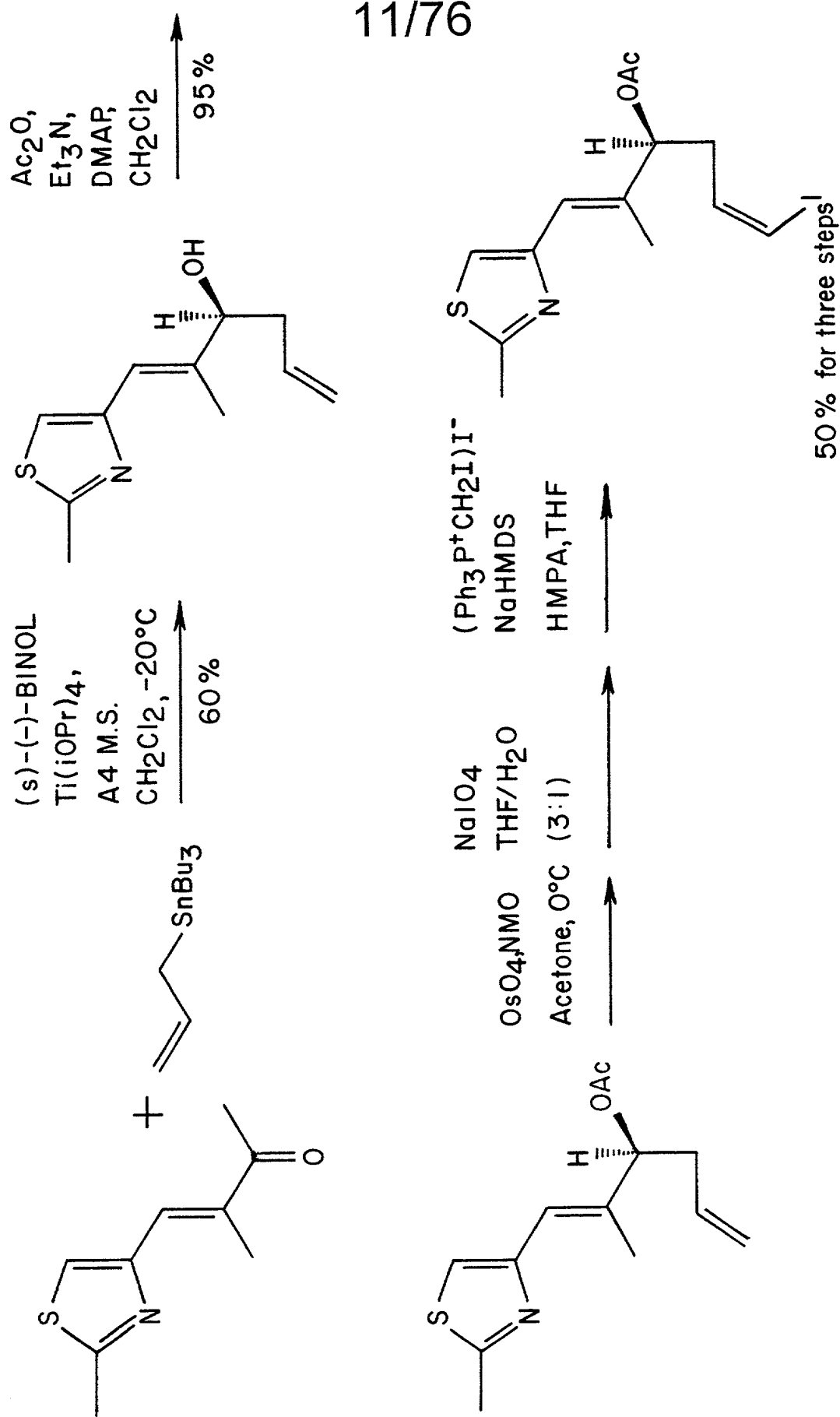


FIG. 6A

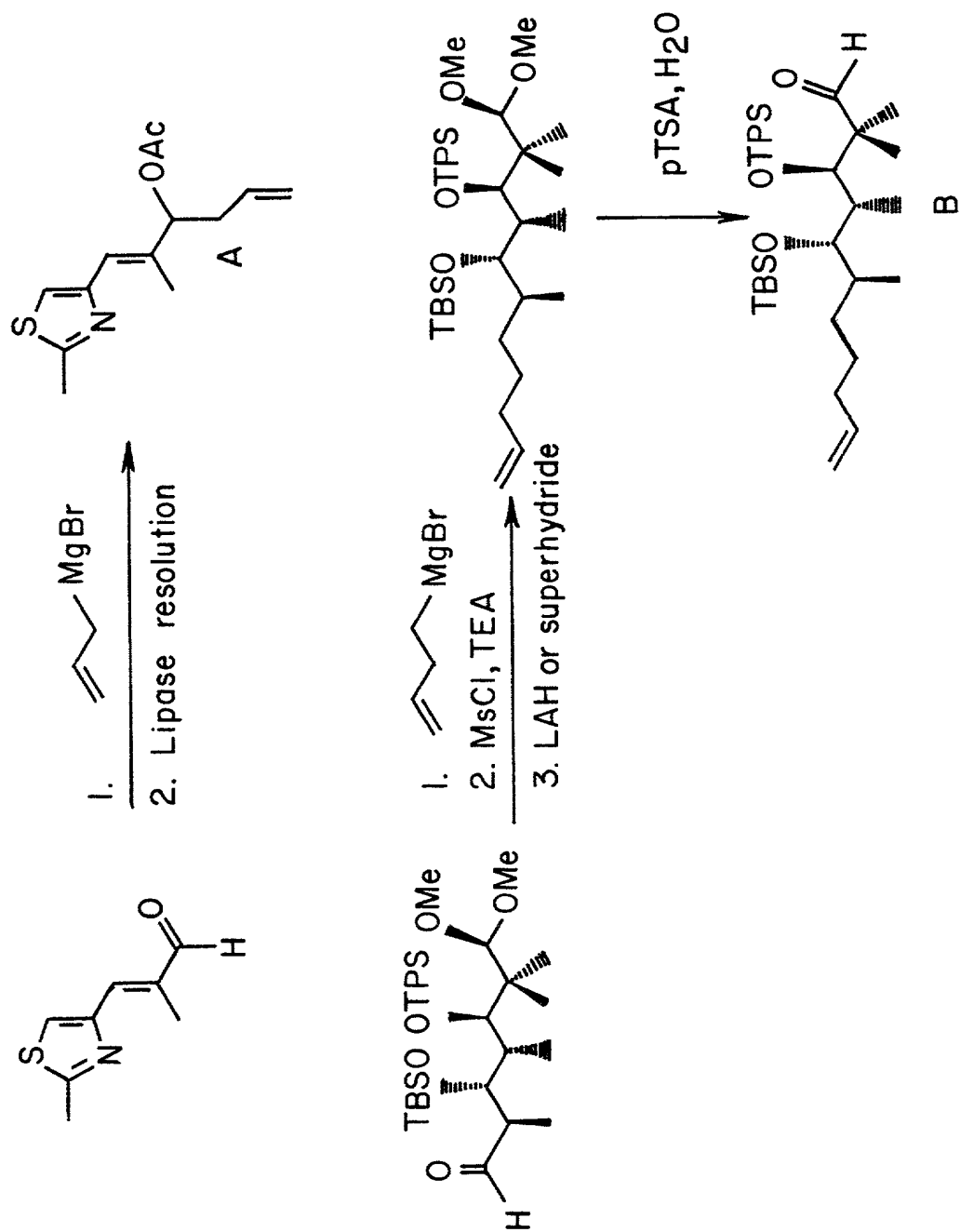
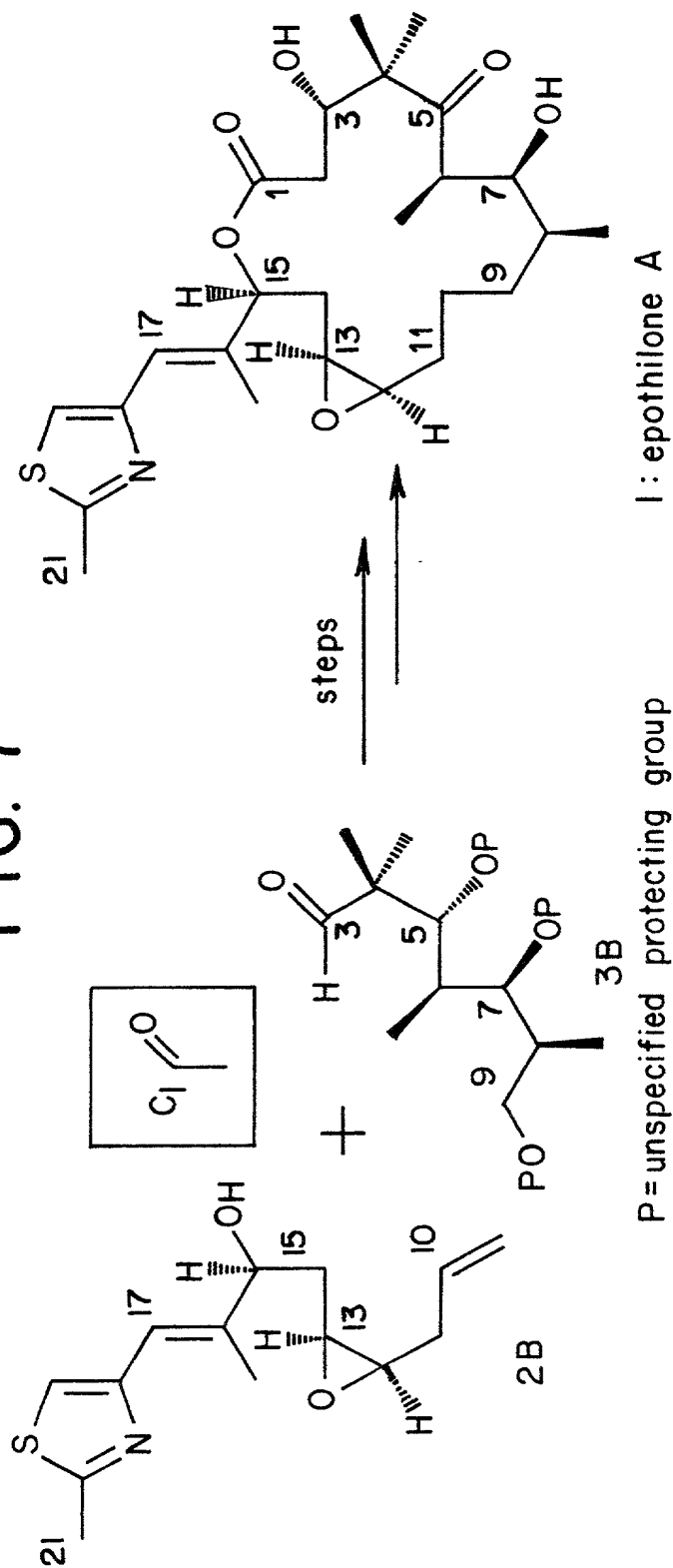
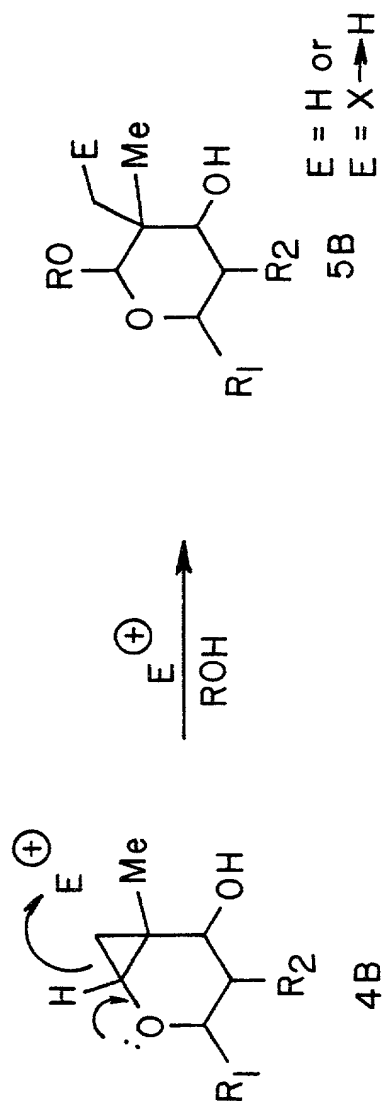


FIG. 7



P = unspecified protecting group 1: epothilone A



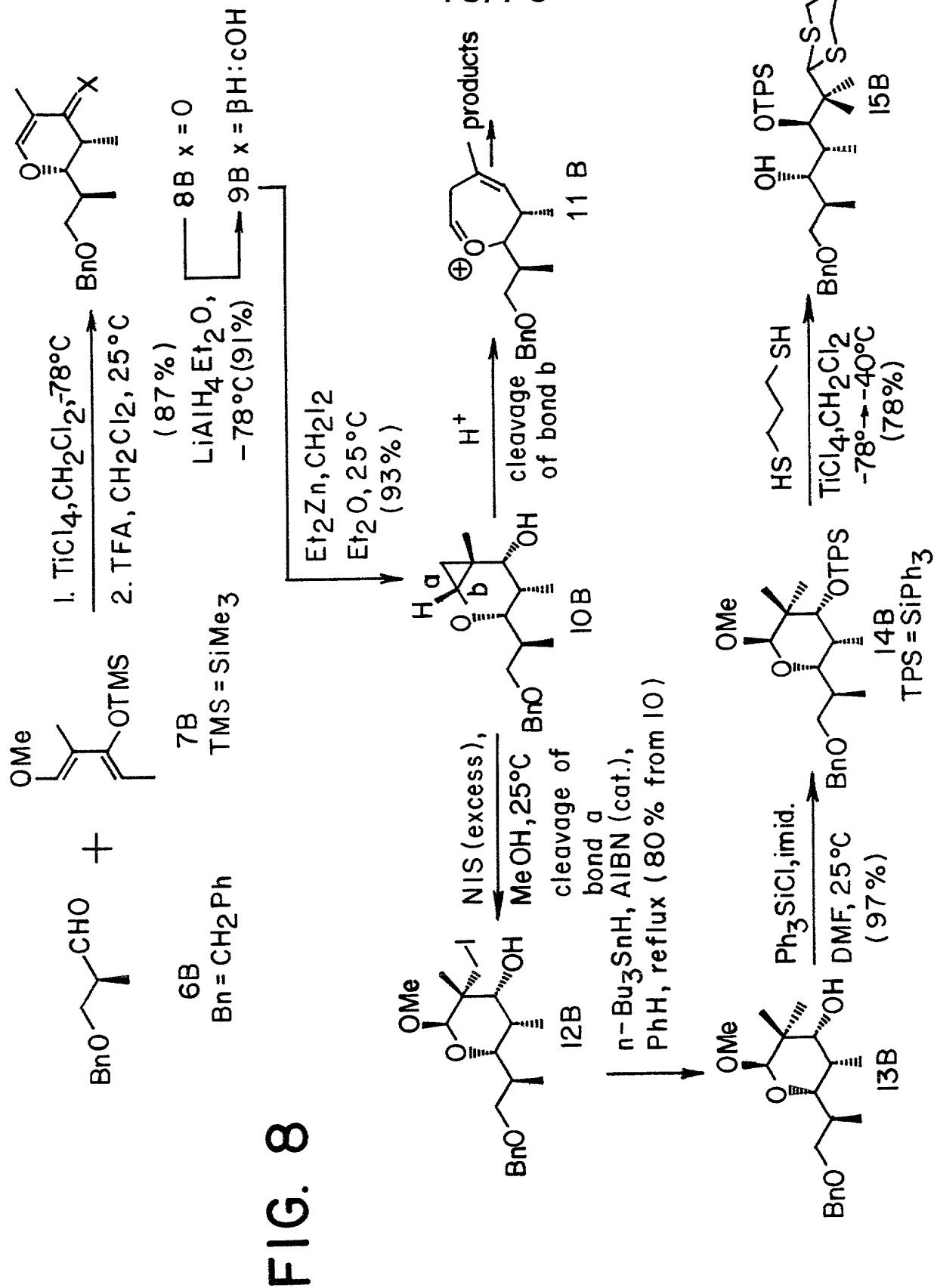
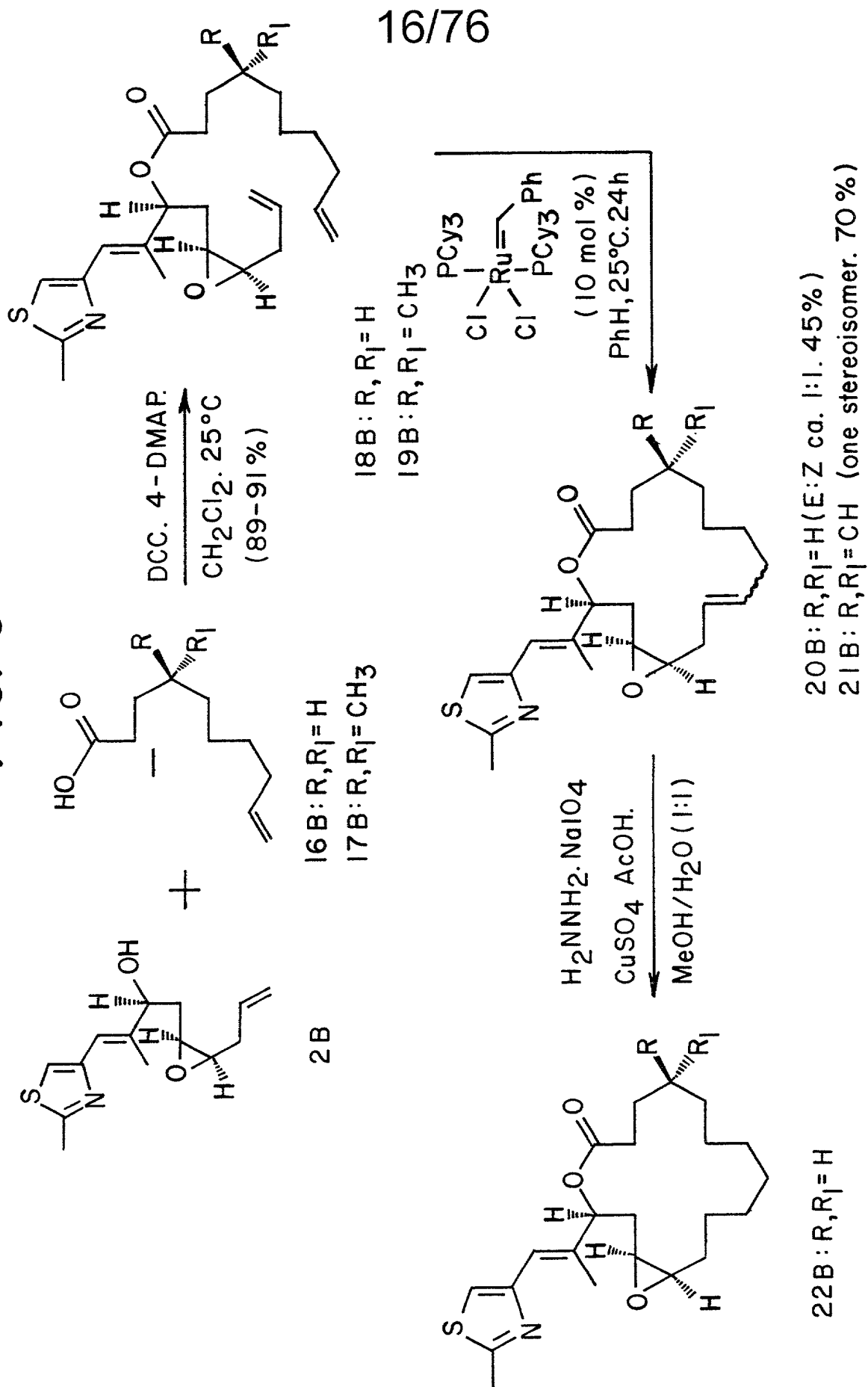
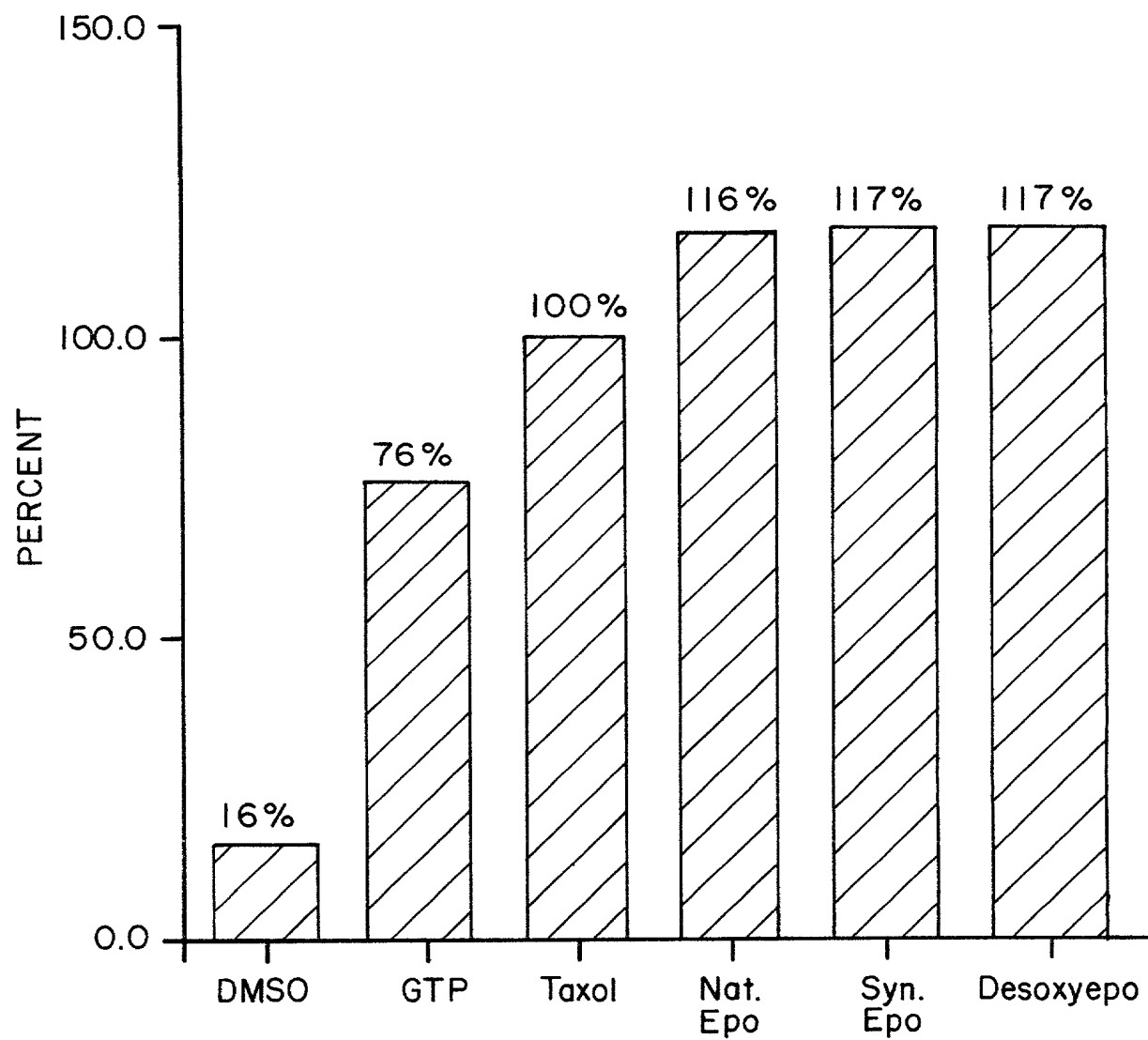


FIG. 9



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FIG. 10



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FIG. II

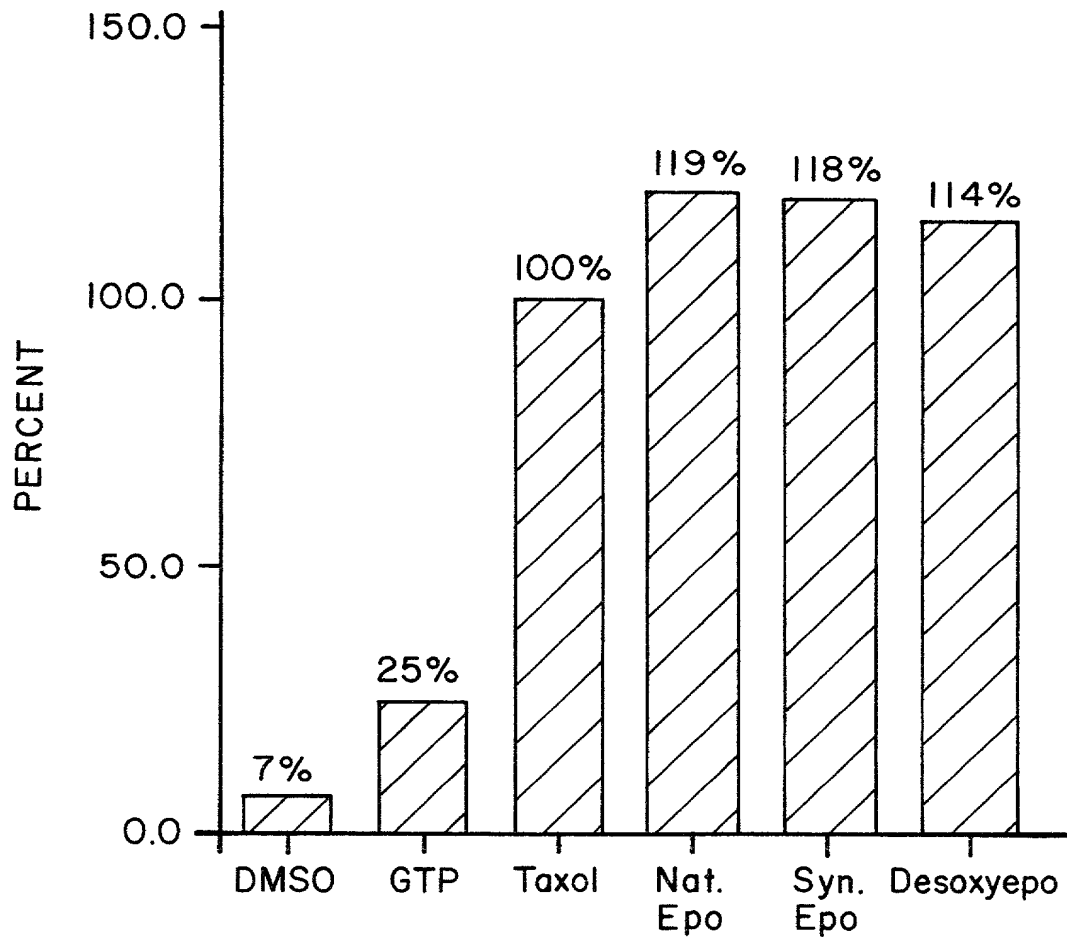


FIG. 13

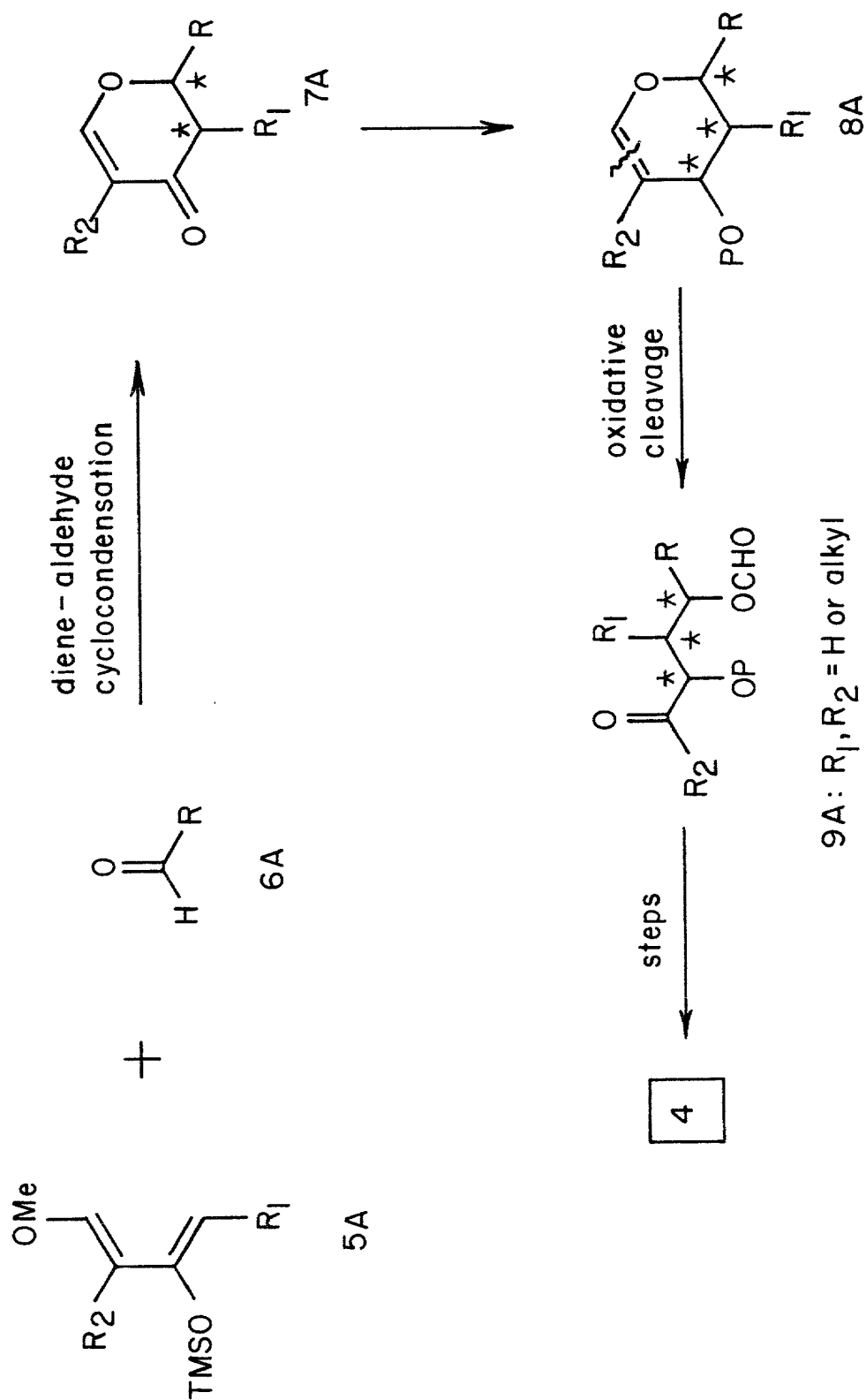
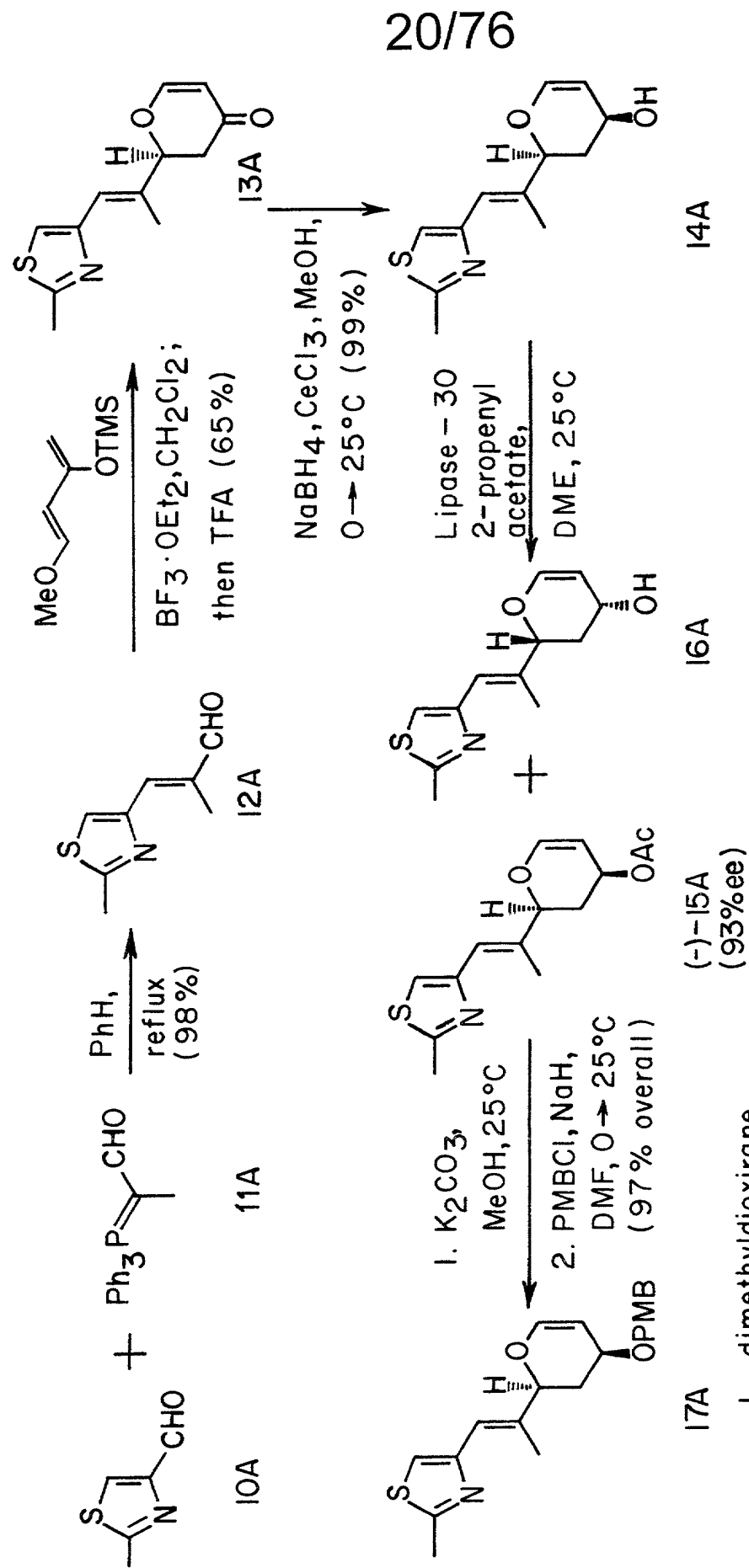


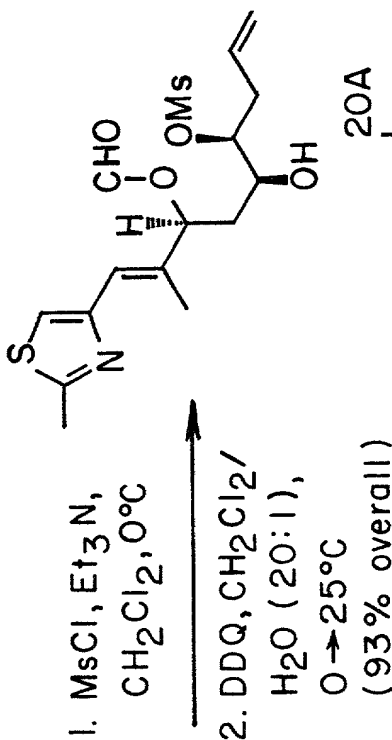
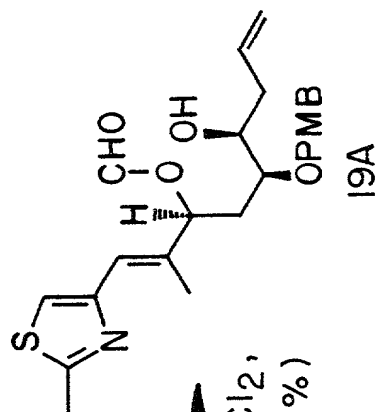
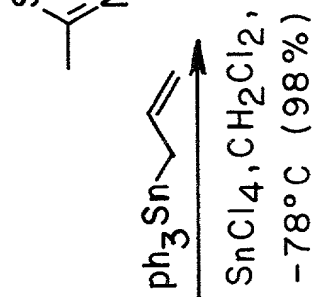
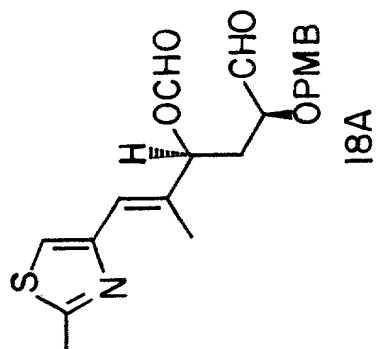
FIG. 14A



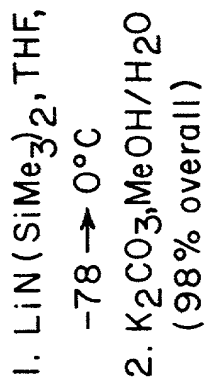
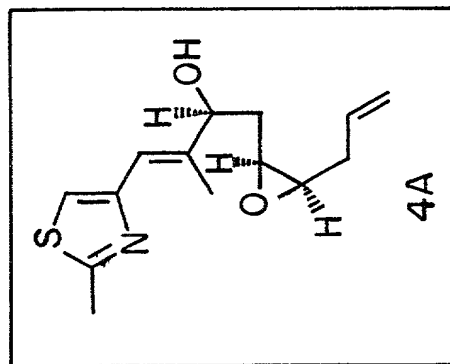
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A — A

FIG. 14B



20A



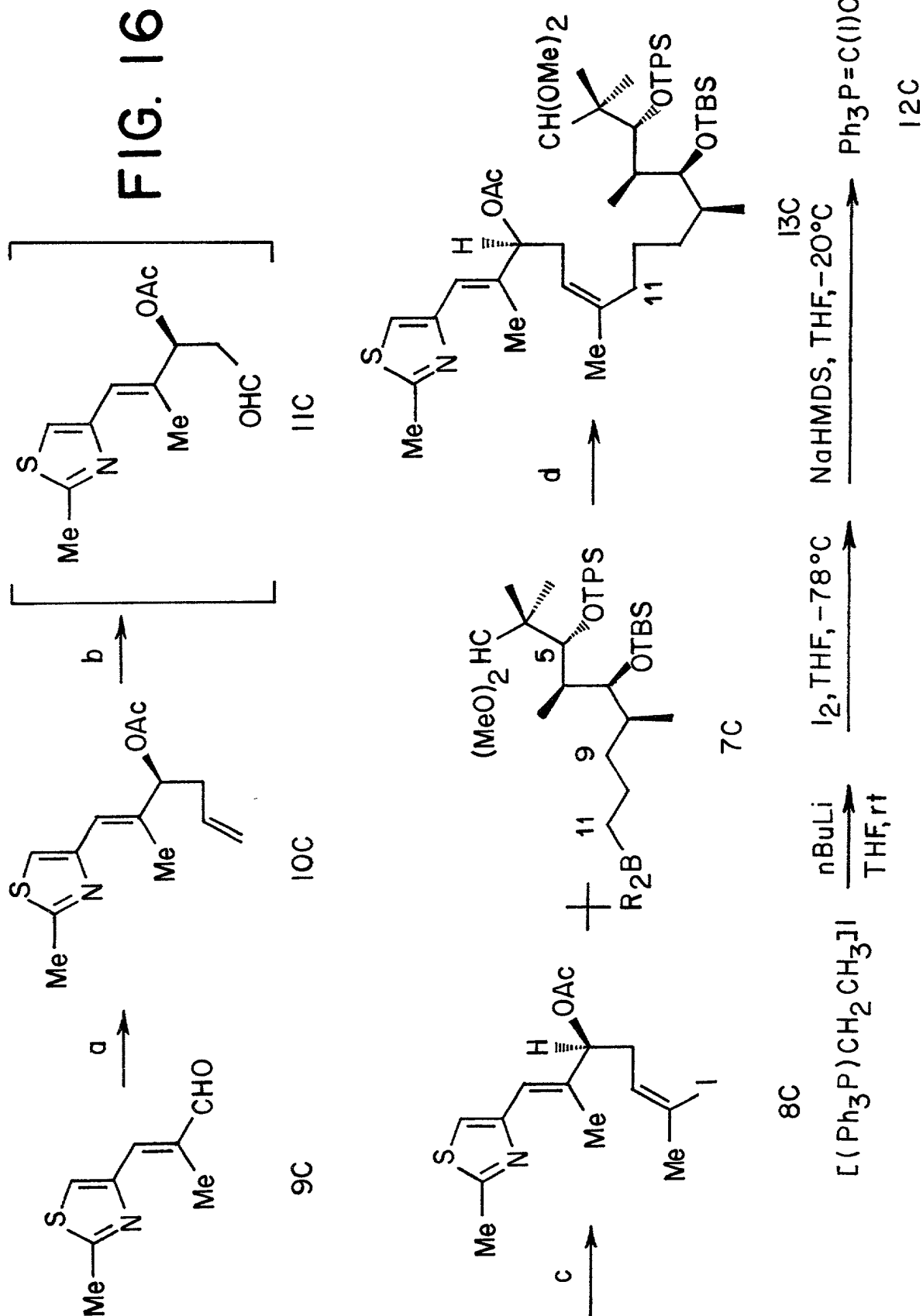
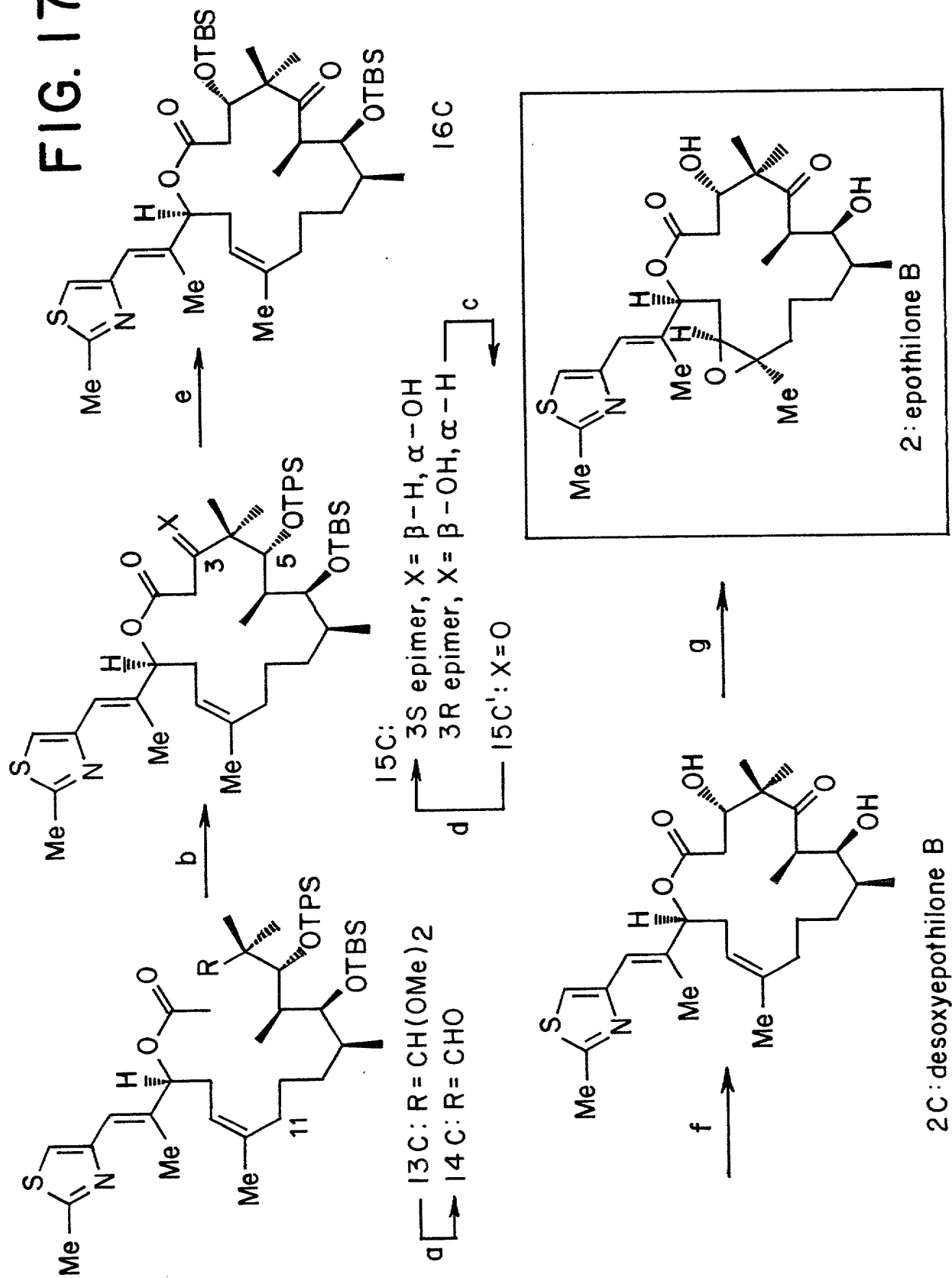


FIG. 17



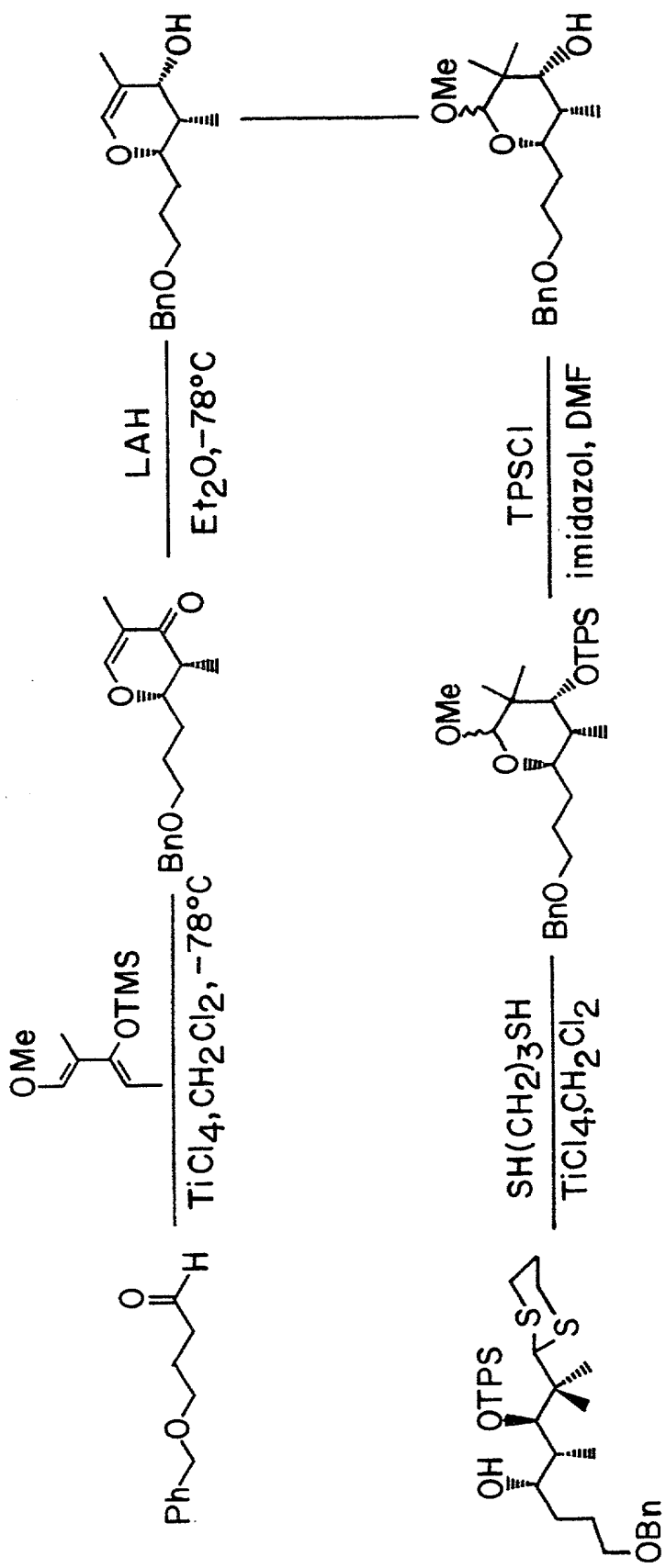


FIG. 18 A

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FIG. 18B

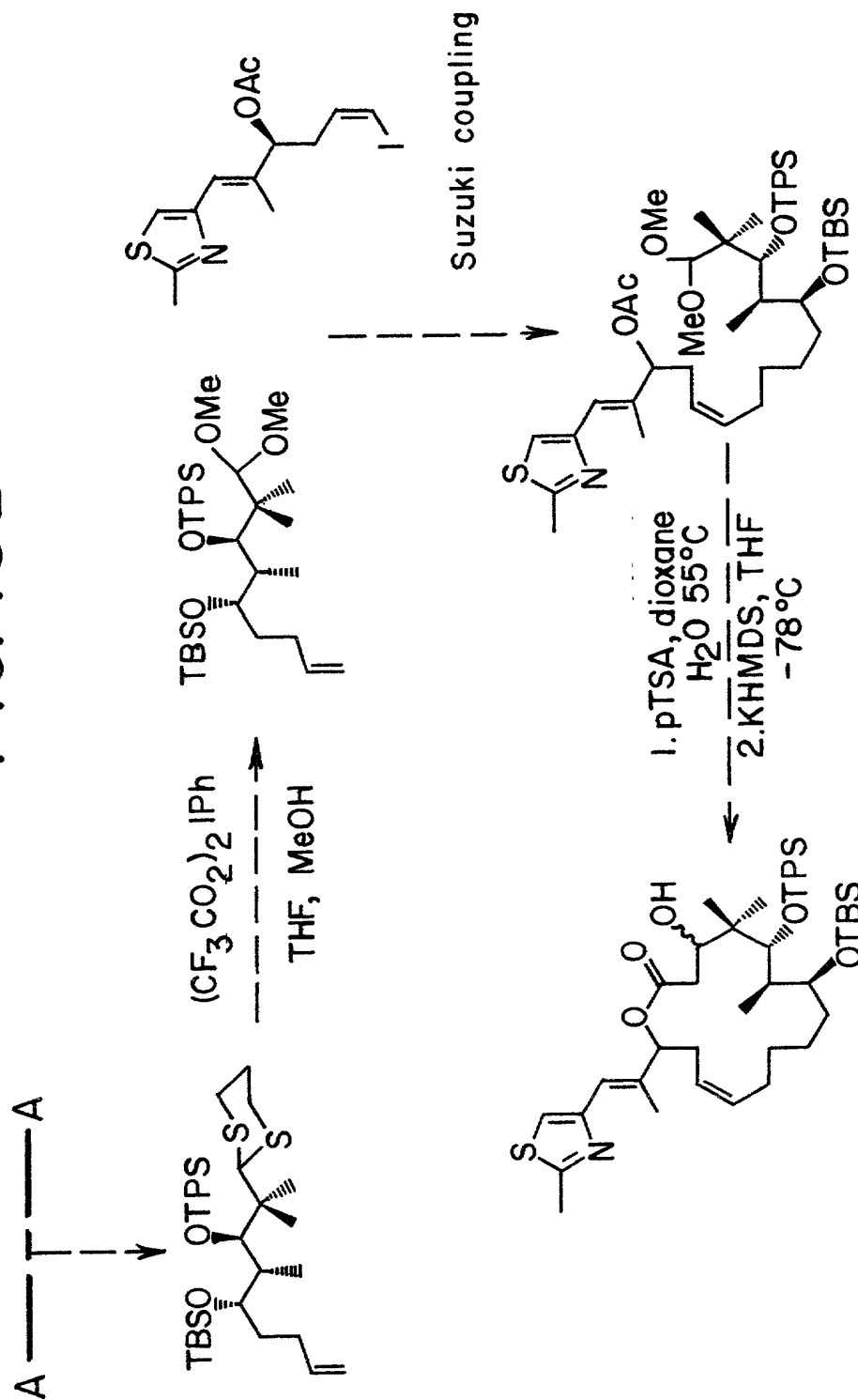


FIG. 19A

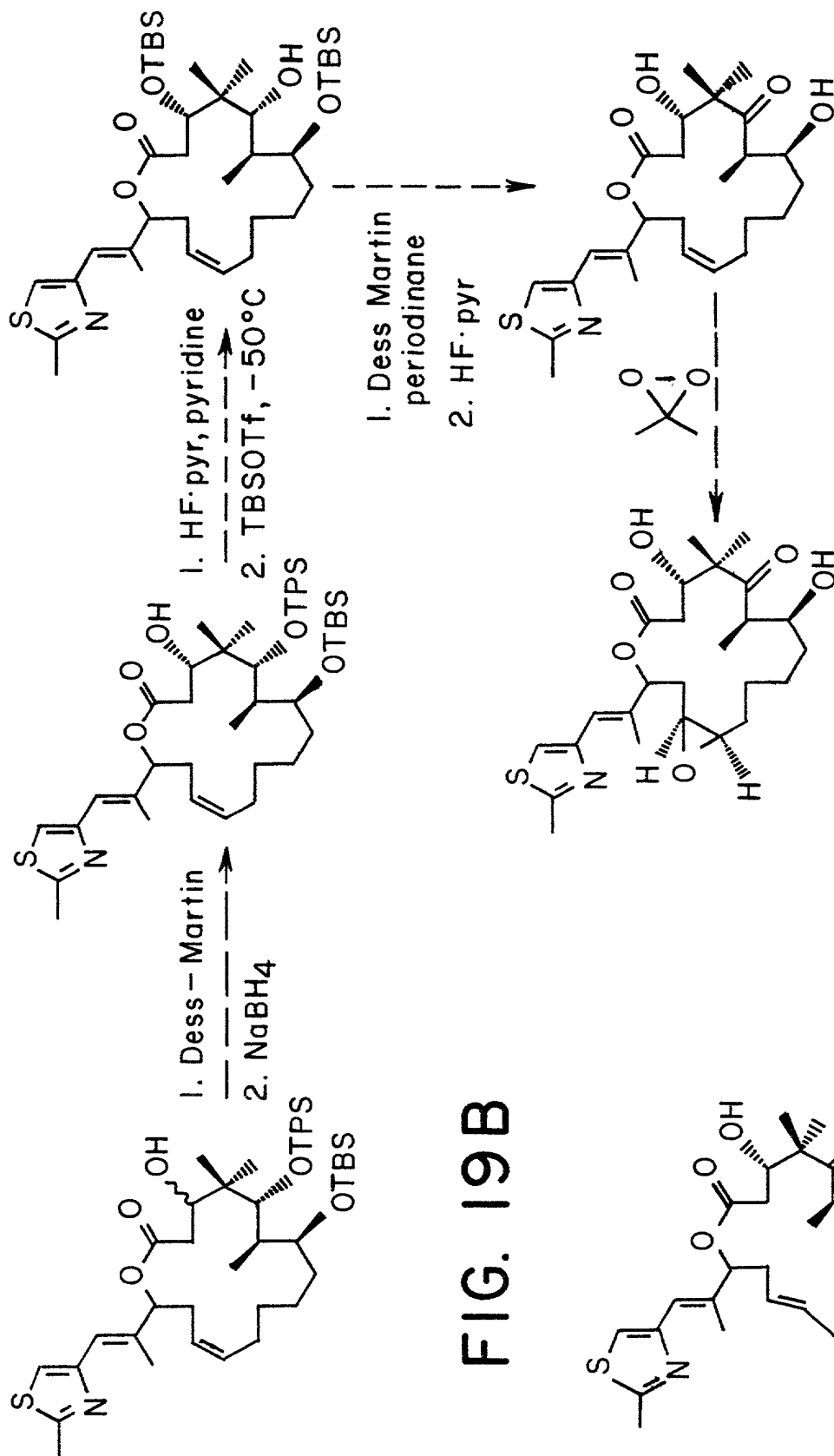
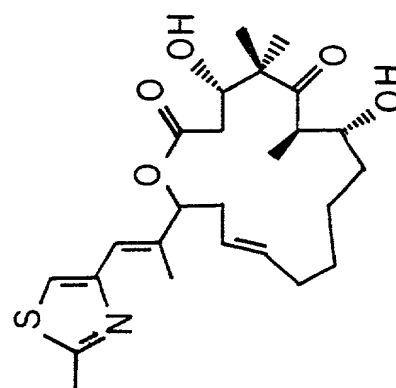


FIG. 19B



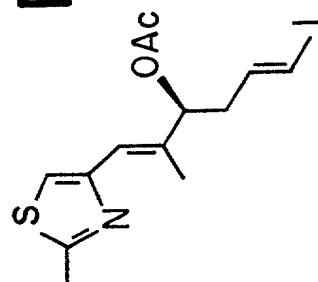


FIG. 19C

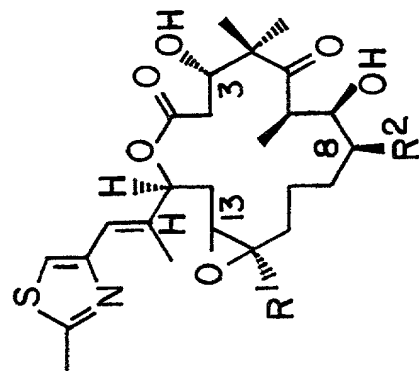
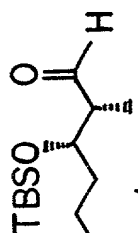
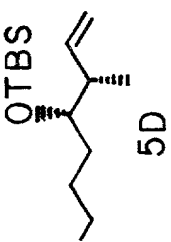
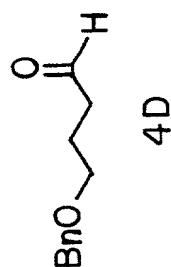


FIG. 20A

$R^1 = H, R^2 = Me$; epothilone A

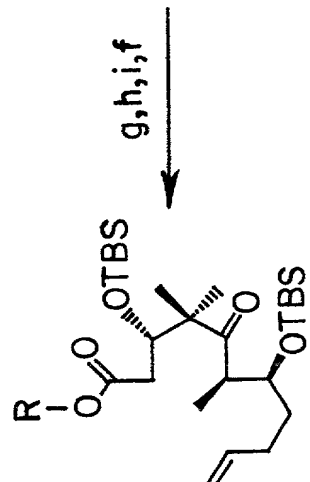
$R^1 = R^2 = Me$; epothilone B

$R^1 = R^2 = H$; C₈-desmethyl-epothilone A (3D)

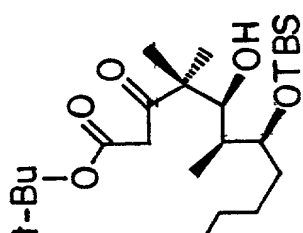
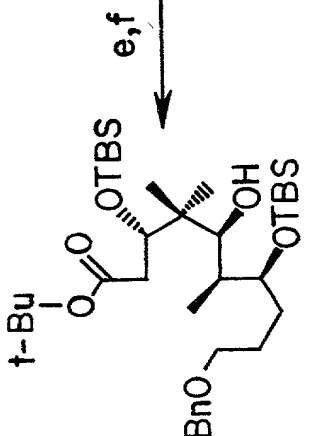


TBS = Sit-buMe₂

FIG. 20B



9D # R = t-butyl/
10D # R = TBS



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FIG. 21

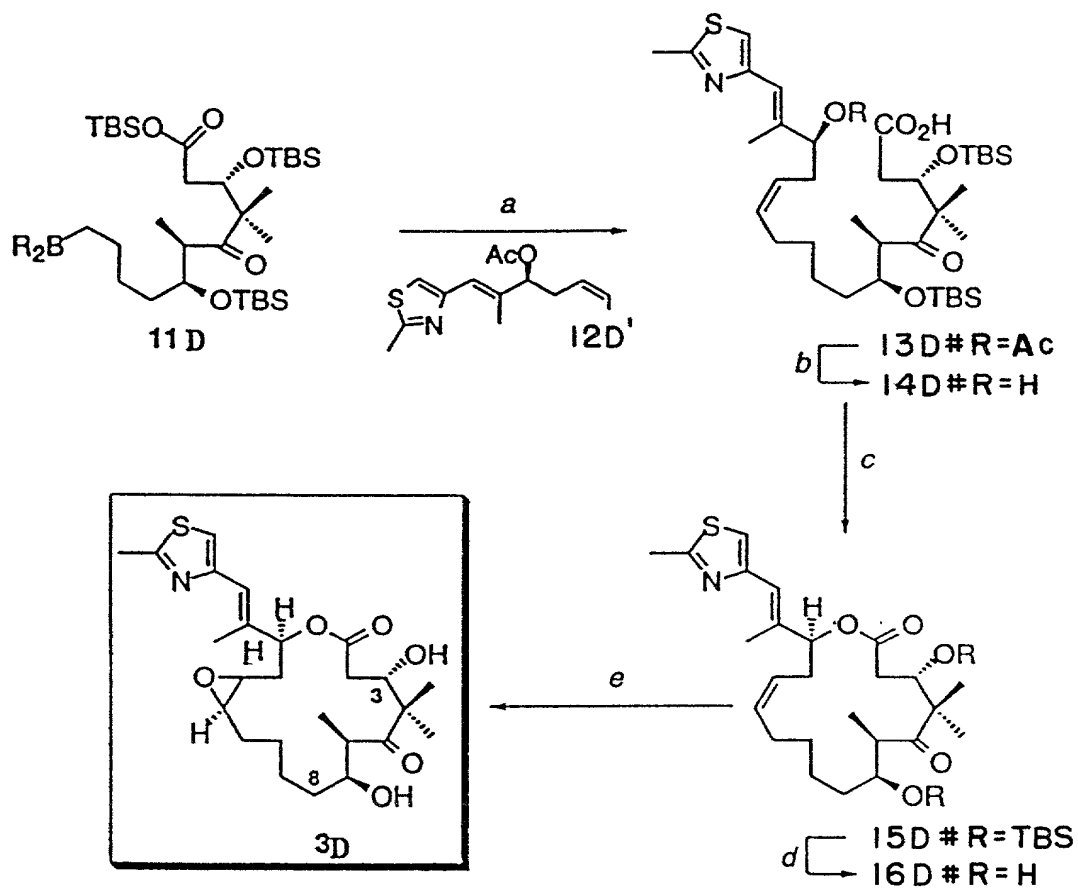


FIG. 22 A

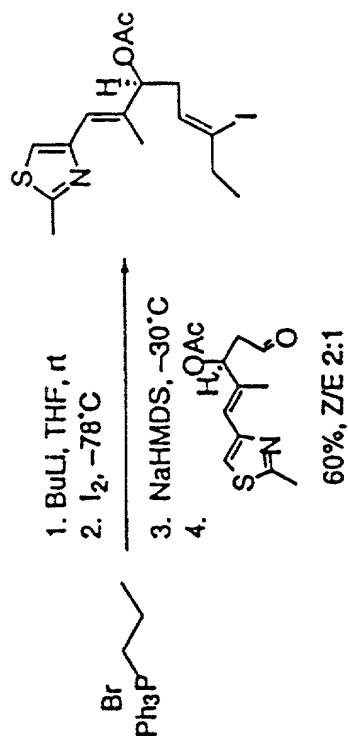


FIG. 22 B

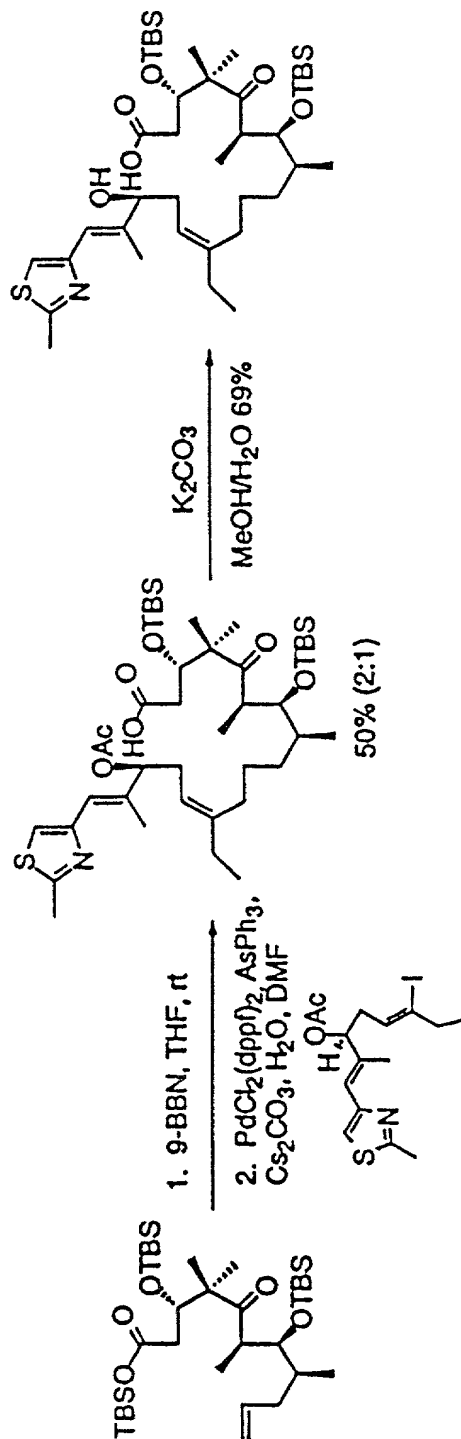


FIG. 22C

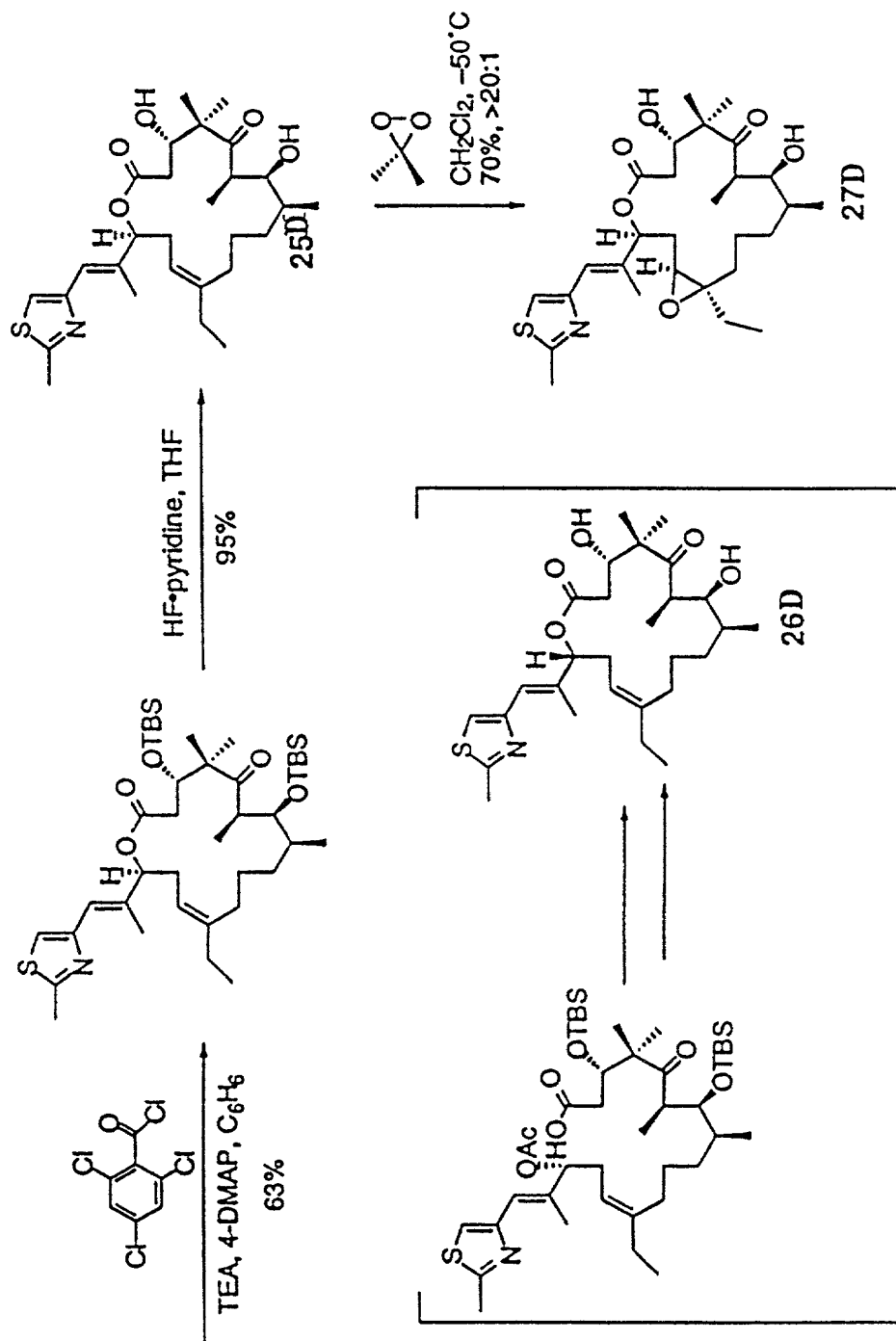


FIG. 23A

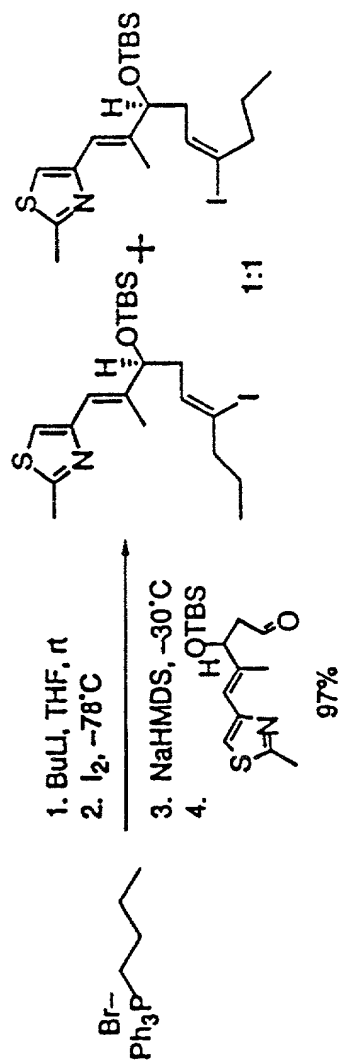


FIG. 23B

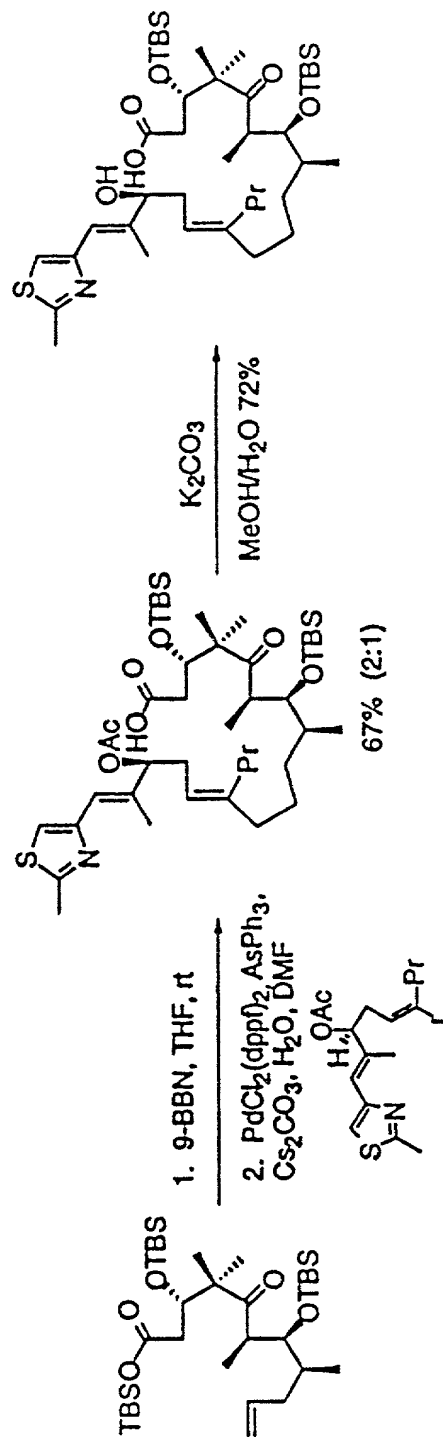


FIG. 23C

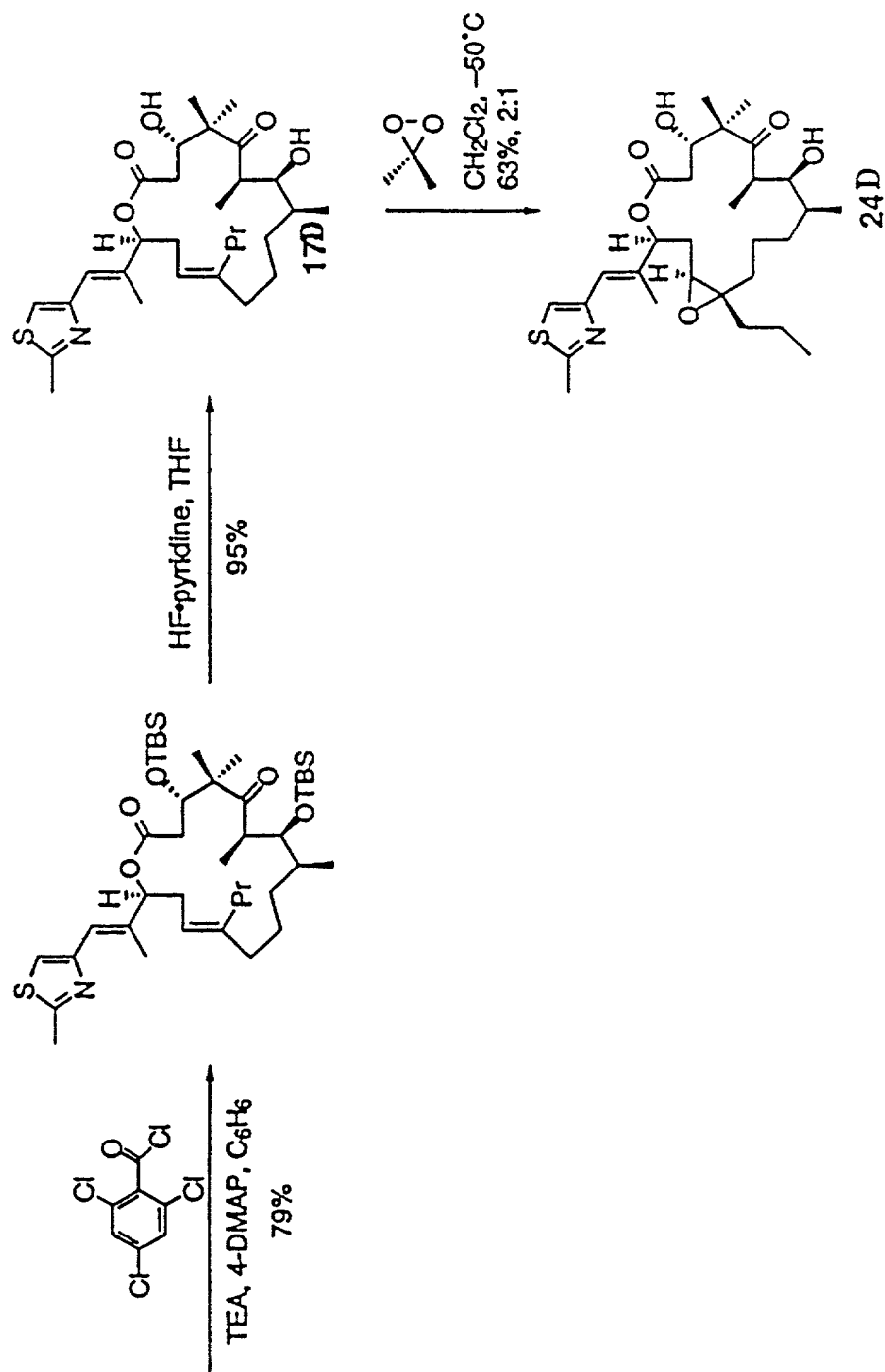
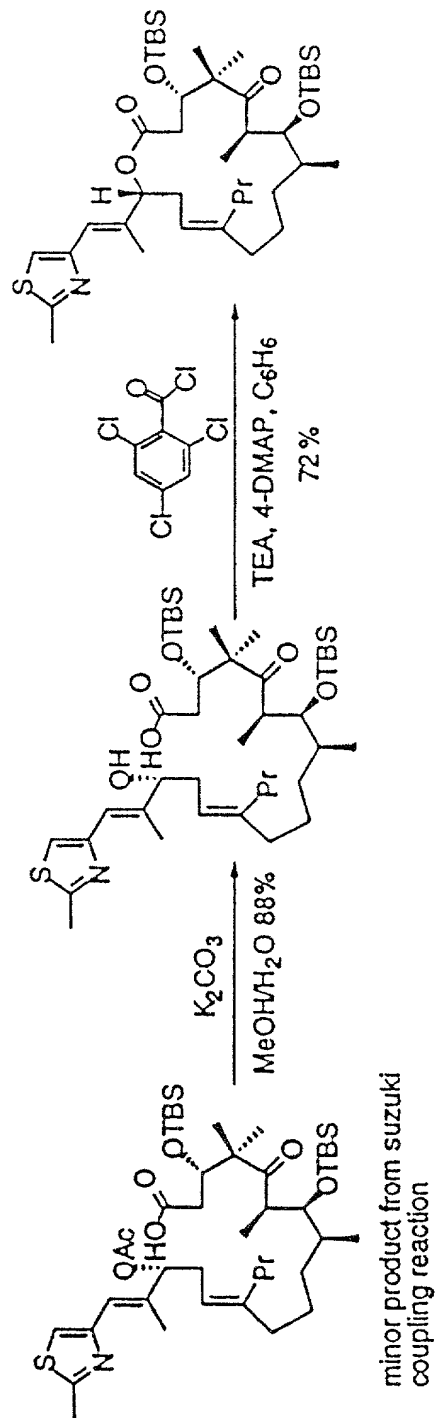


FIG. 24A



minor product from Suzuki coupling reaction

FIG. 24B

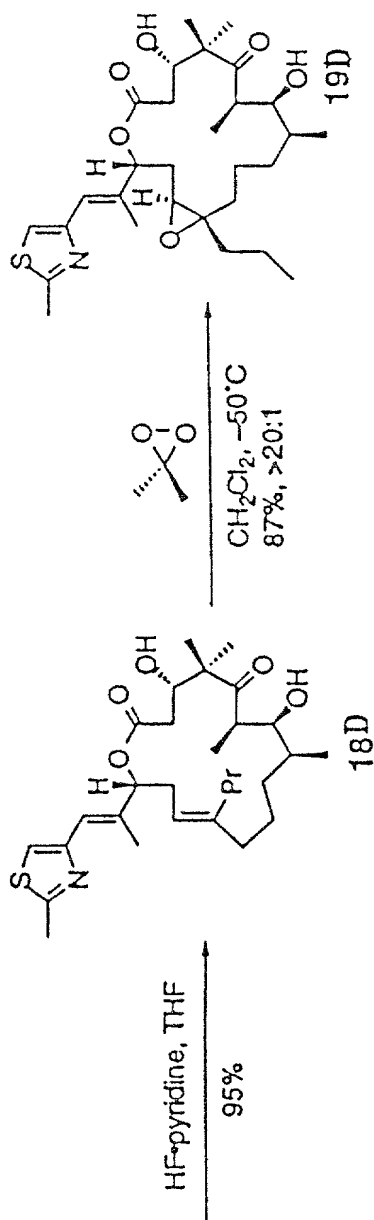


FIG. 25A

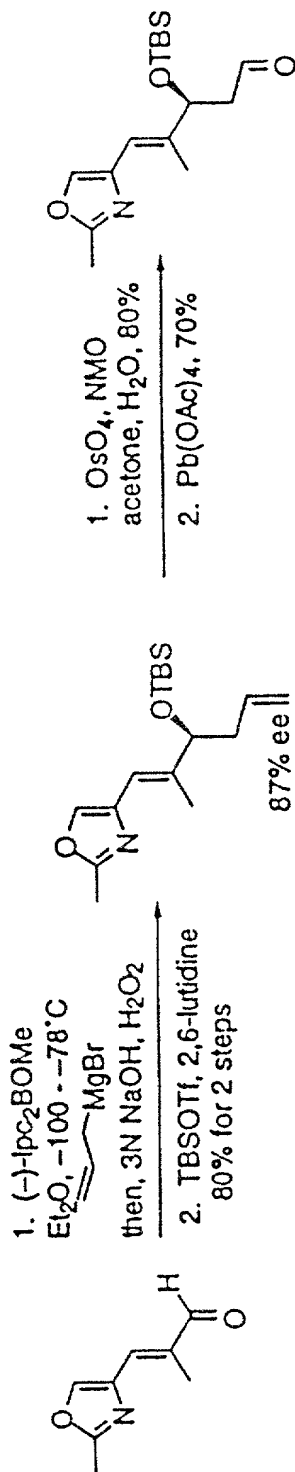


FIG. 25B

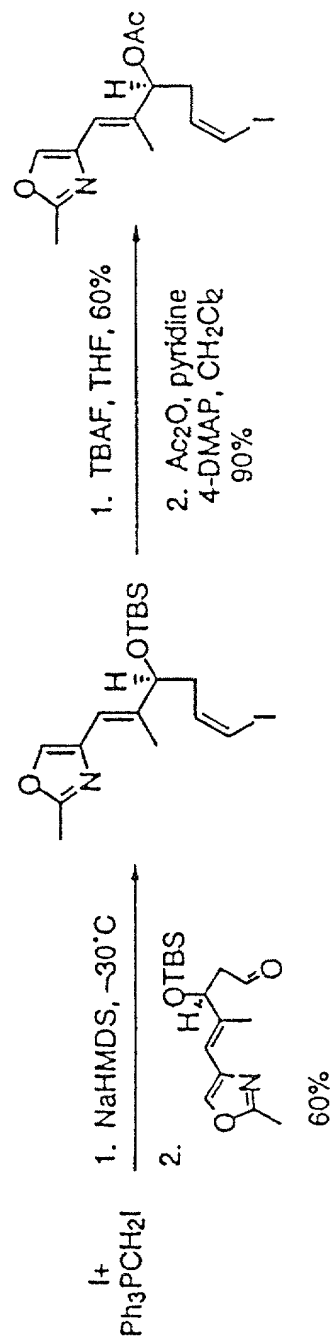


FIG. 25C

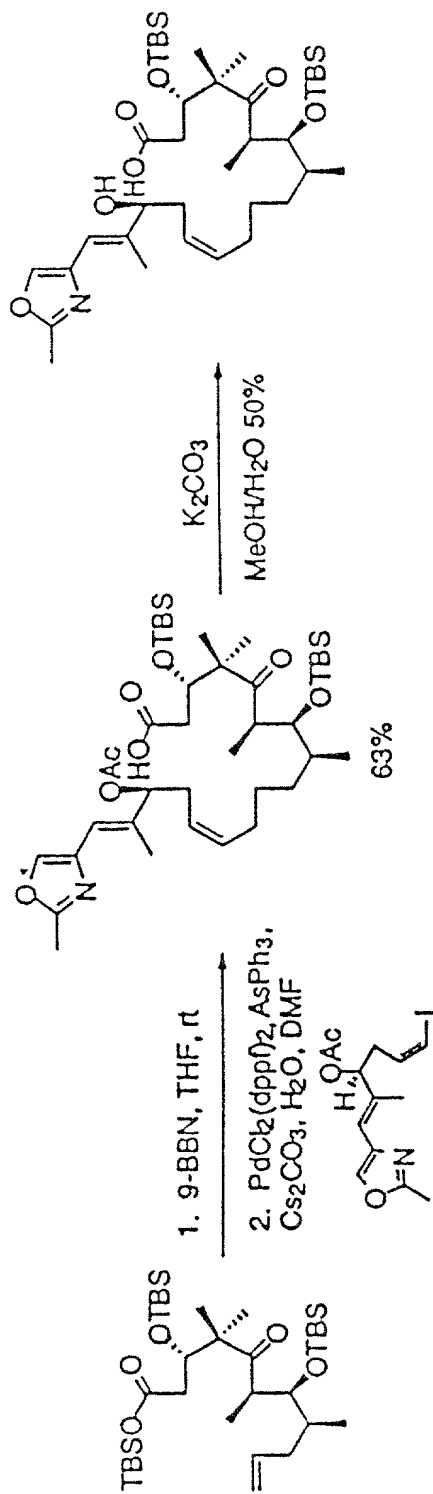


FIG. 25D

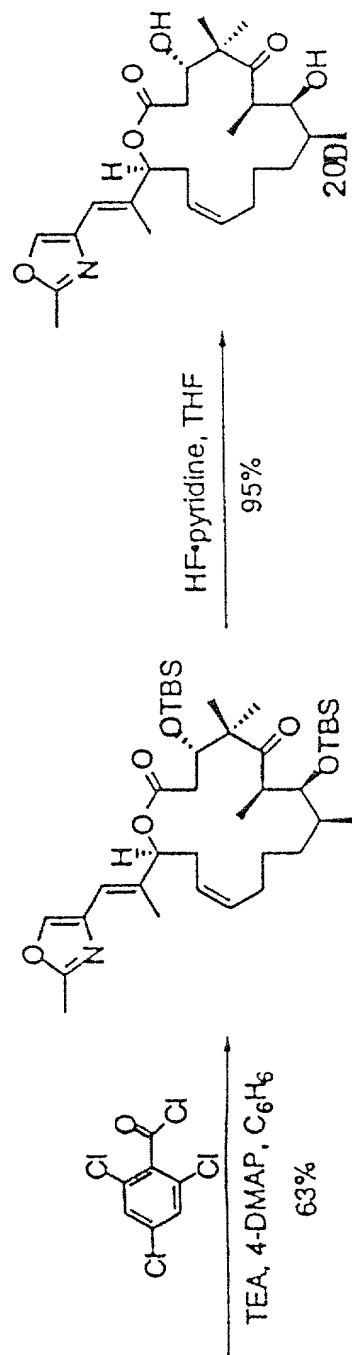


FIG. 26A

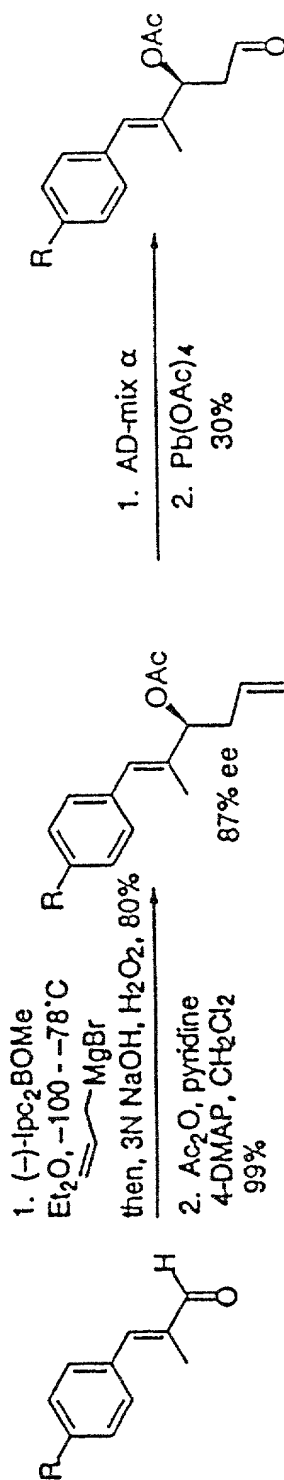
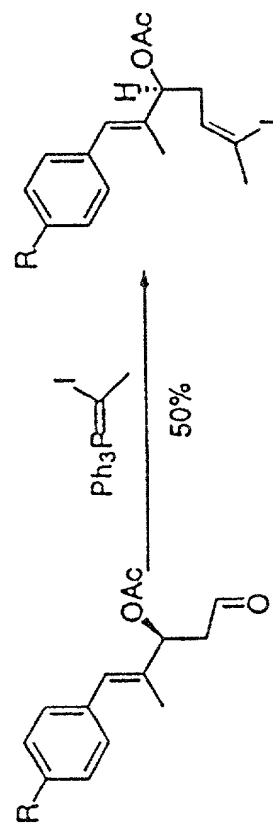


FIG. 26B



R = H, F, CF₃
 R=H is the only compound
 completed, F and CF₃ are nearly
 completed

FIG. 26C

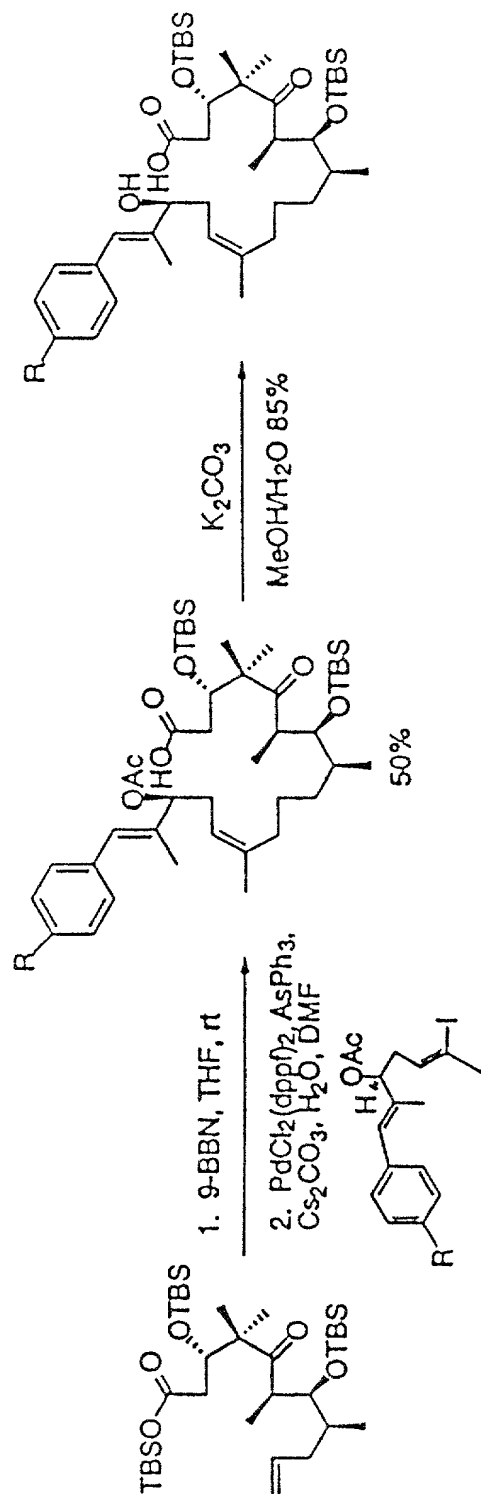


FIG. 26D

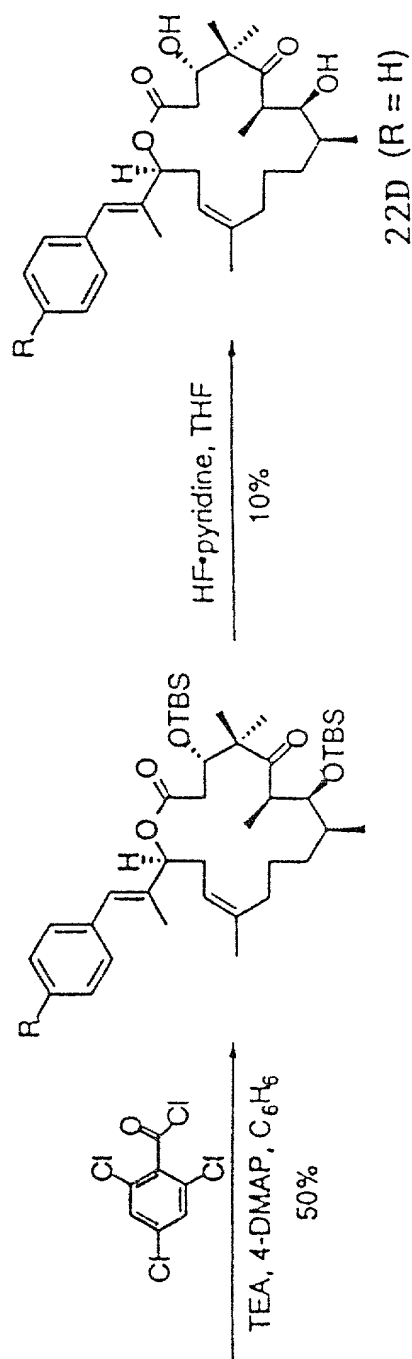


FIG. 27A

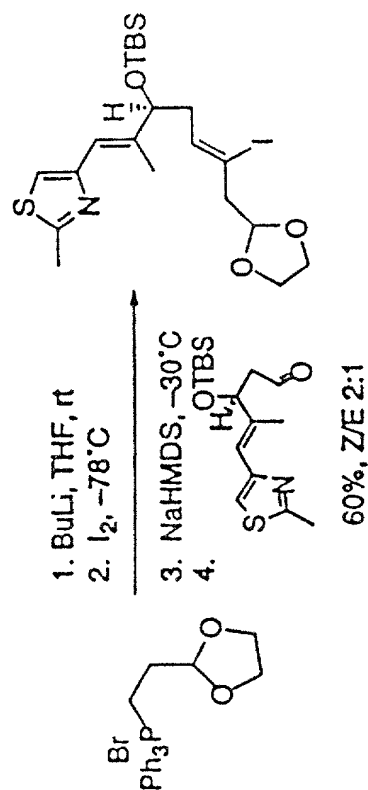


FIG. 27B

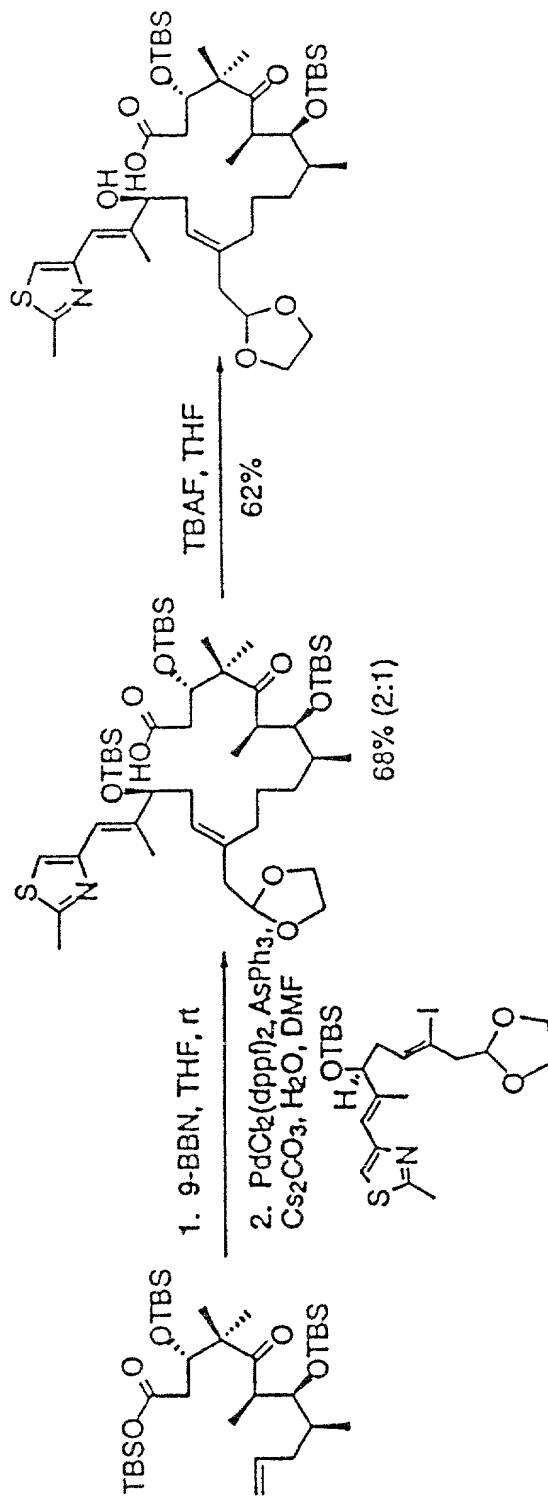
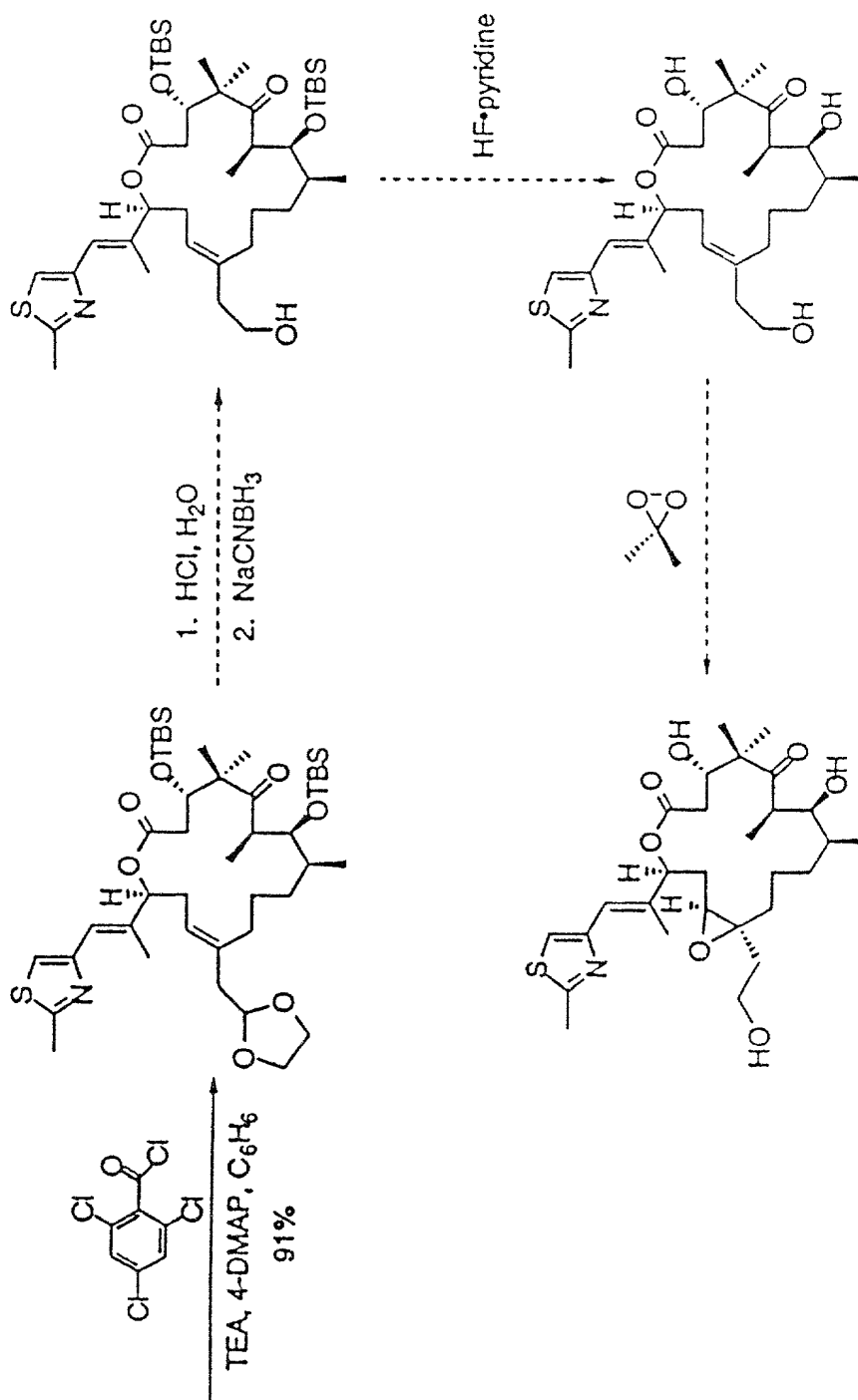


FIG. 27C



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FIG. 28A

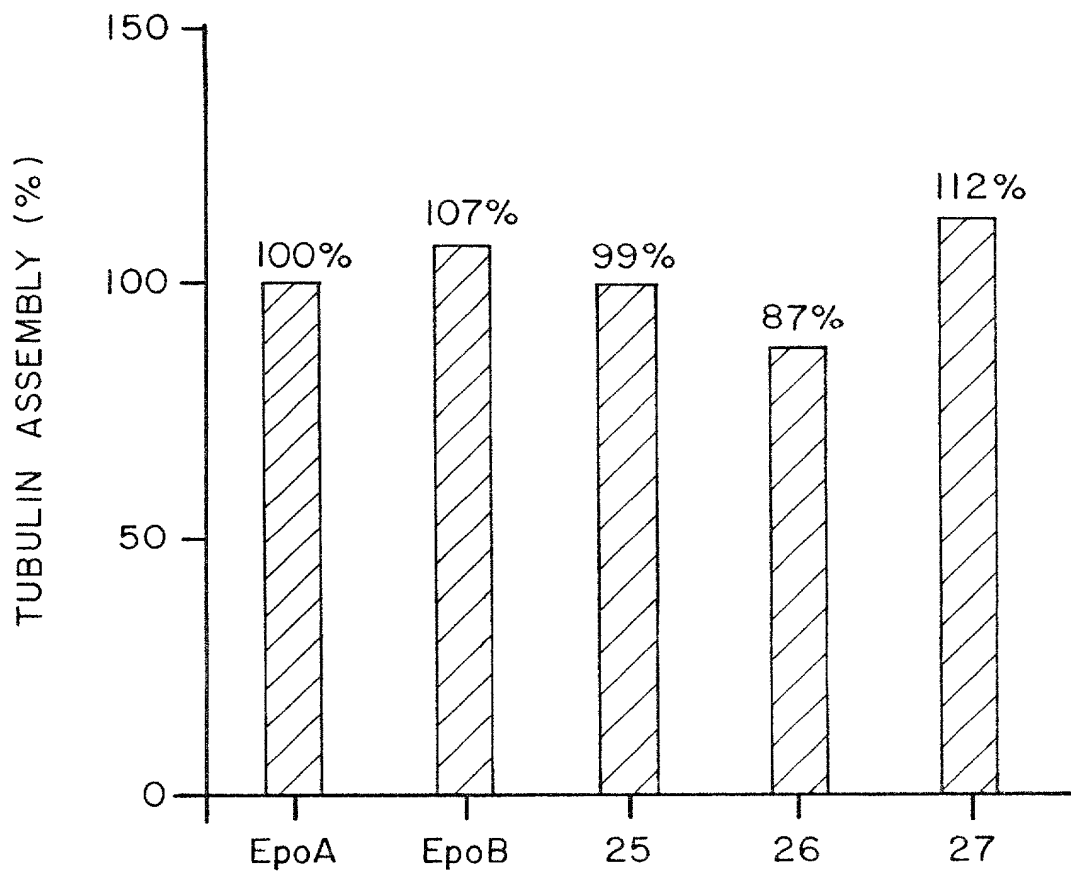
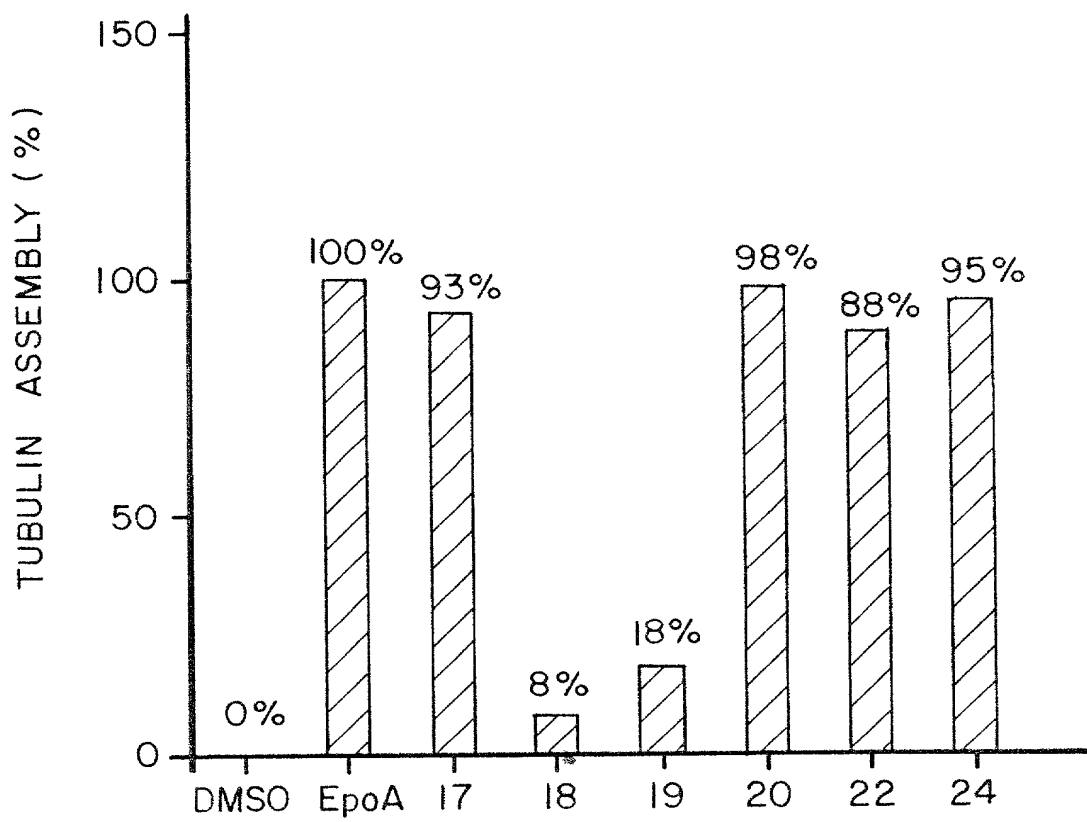


FIG. 28B



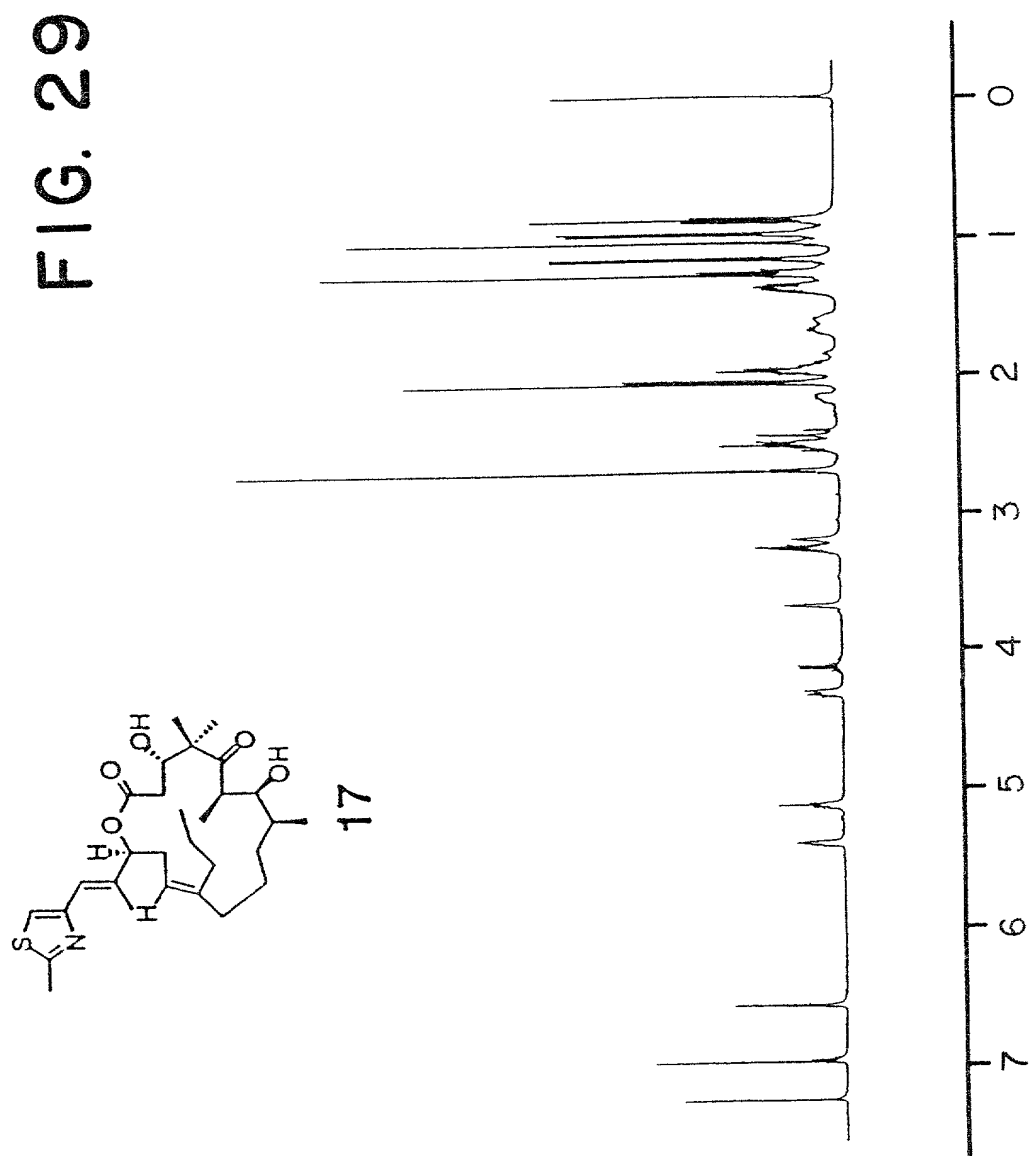


FIG. 30

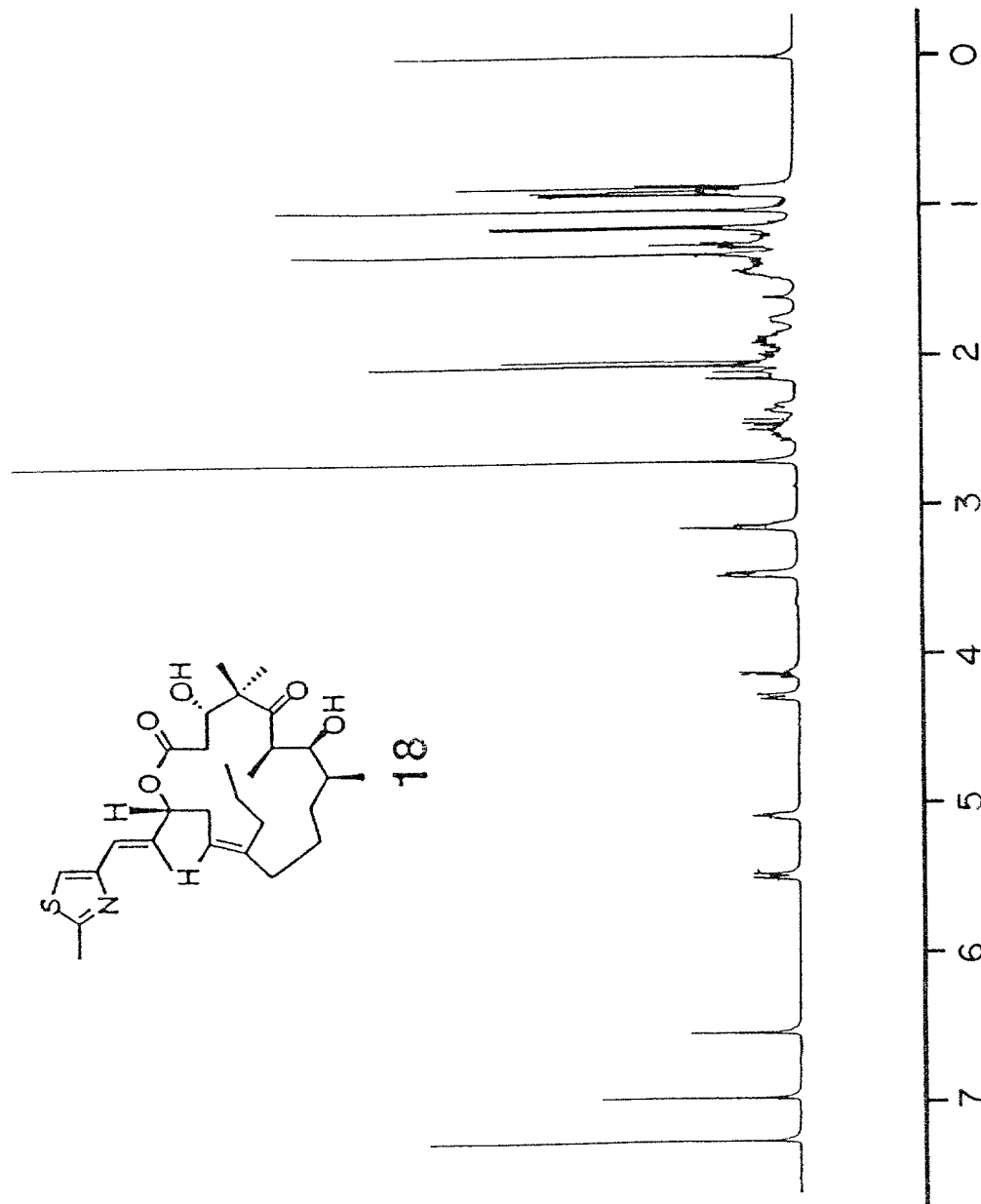


FIG. 31

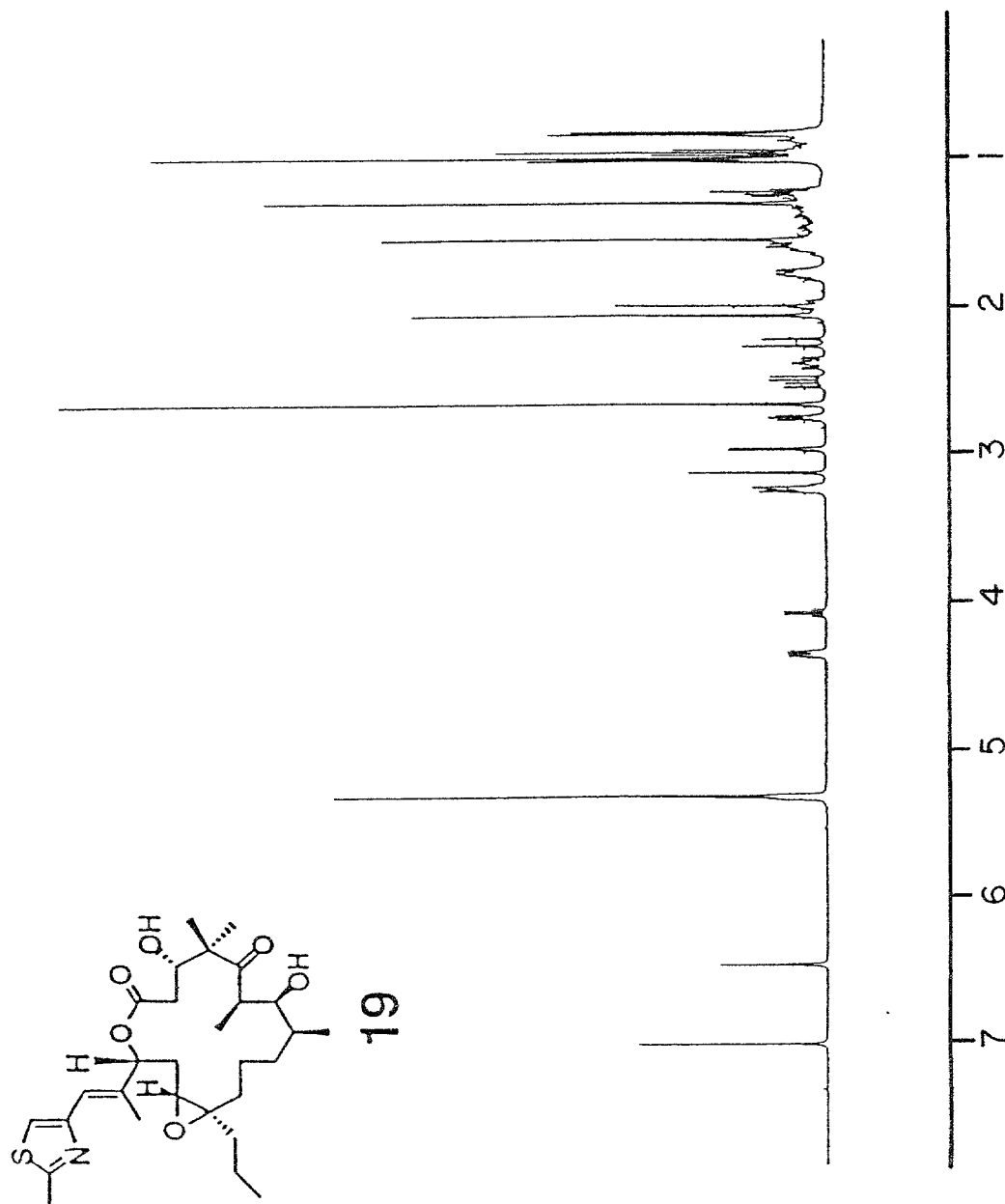


FIG. 32

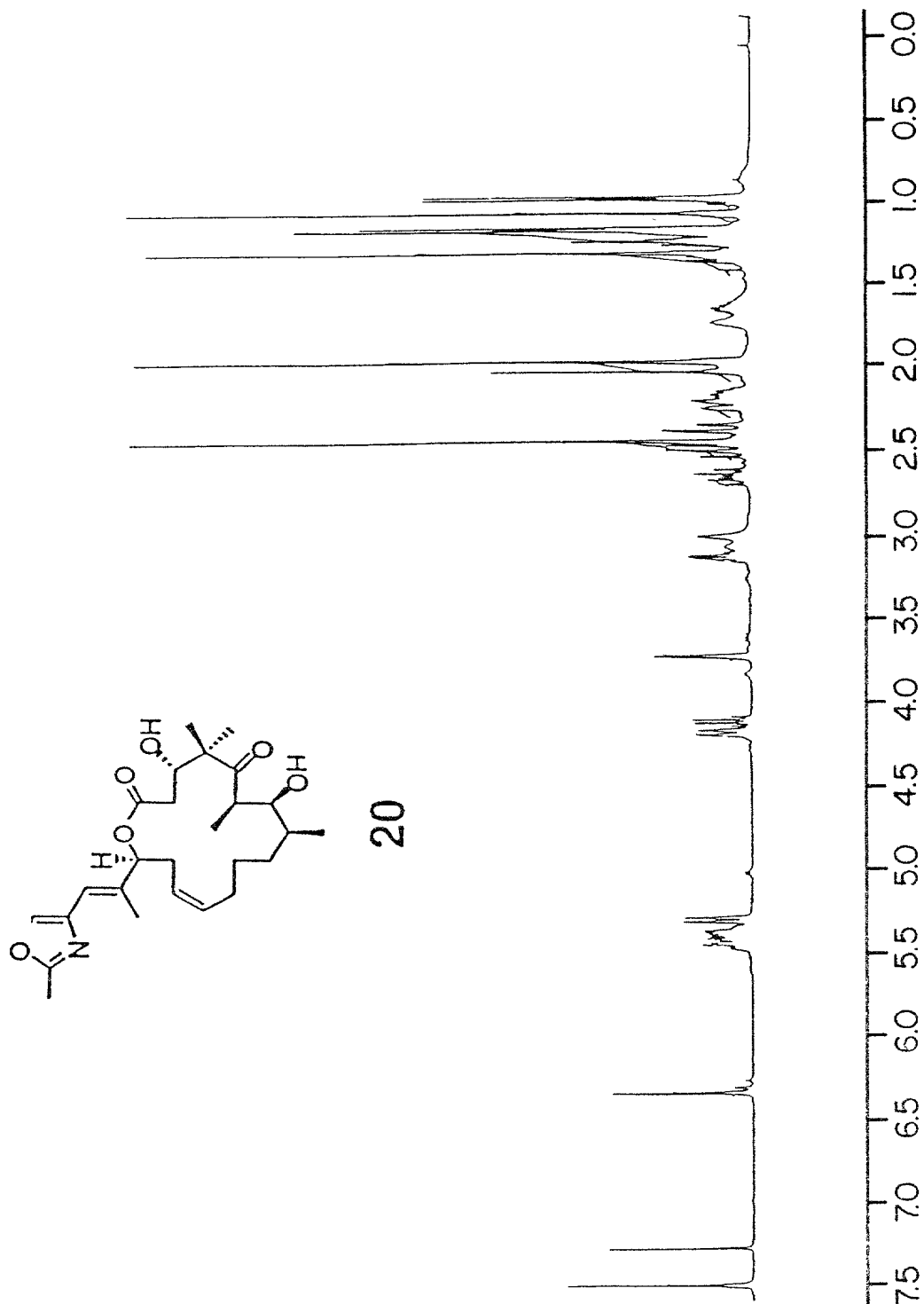


FIG. 33

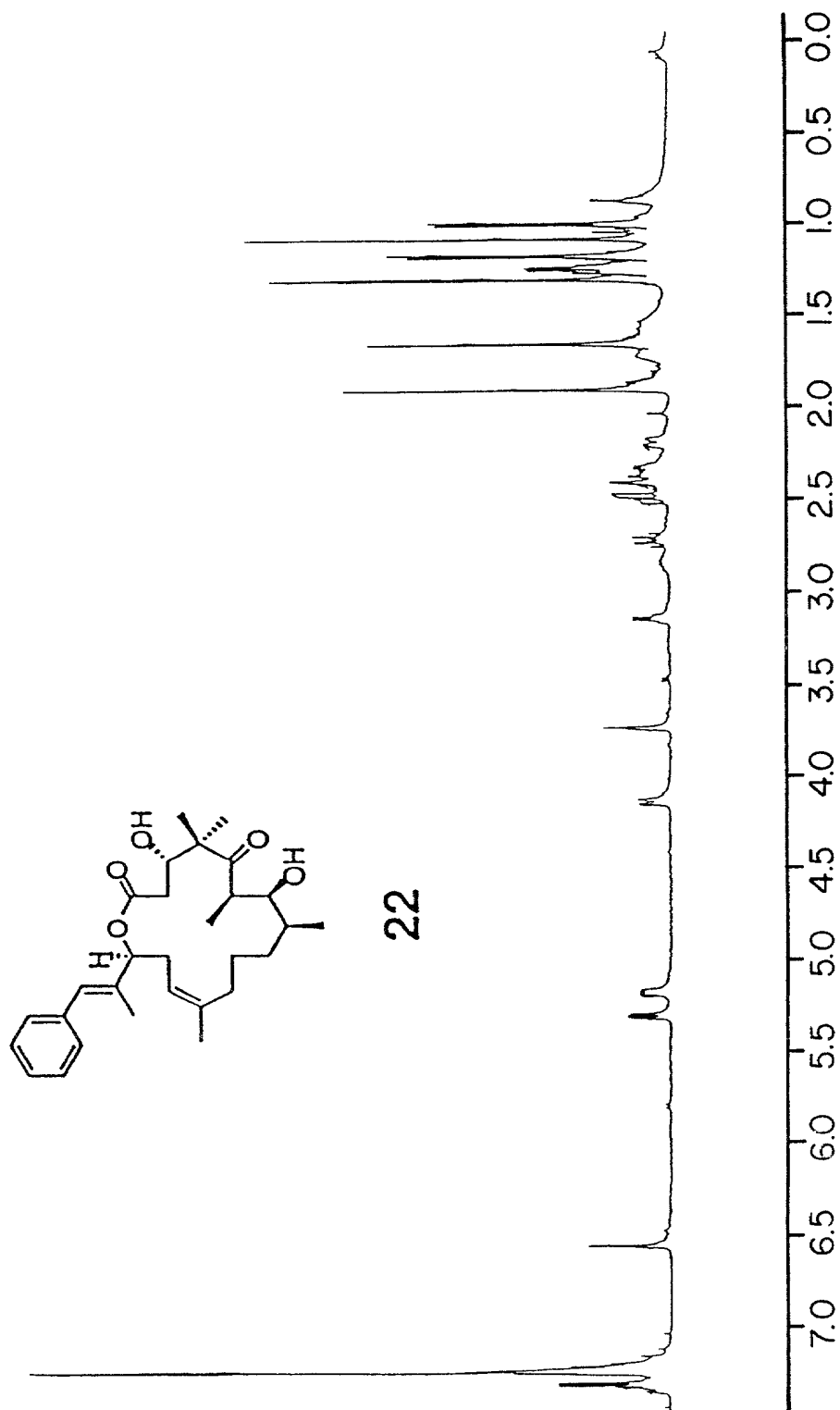
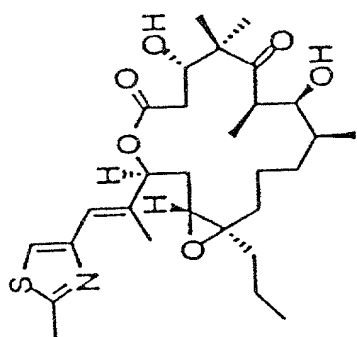
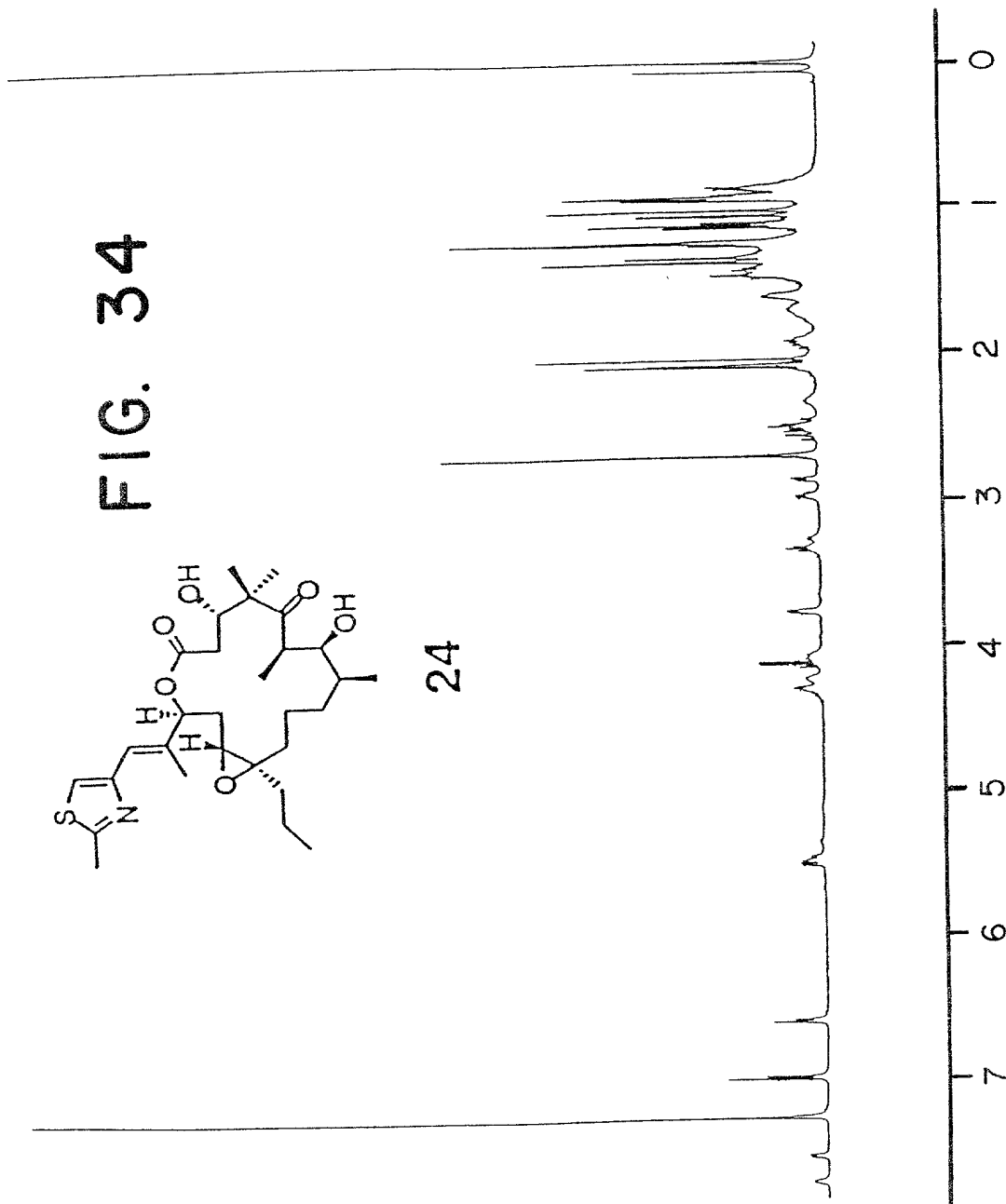


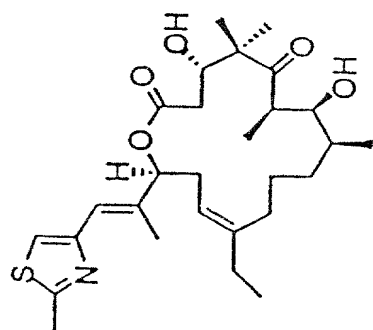
FIG. 34



24



5364



25

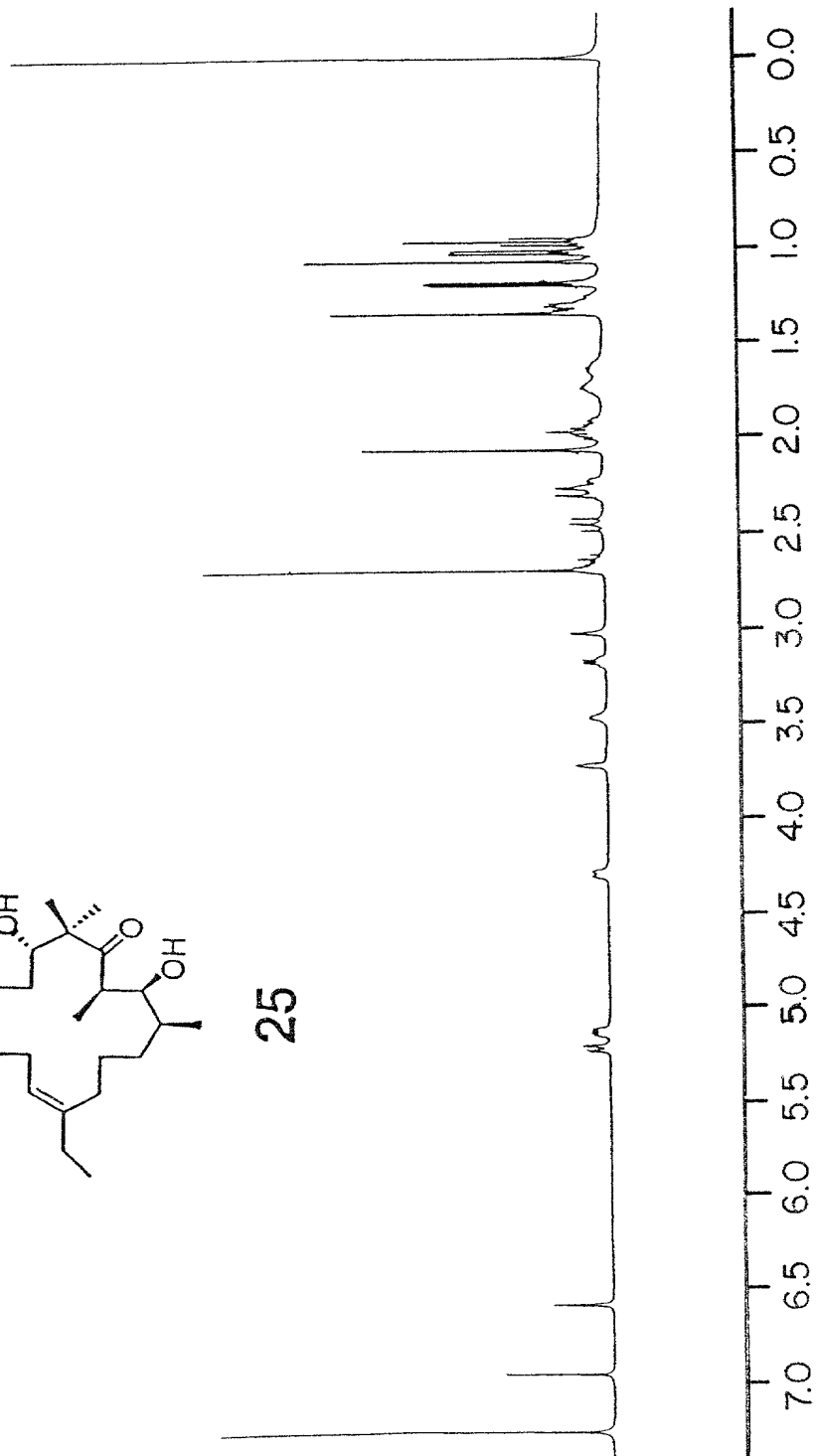


FIG. 36

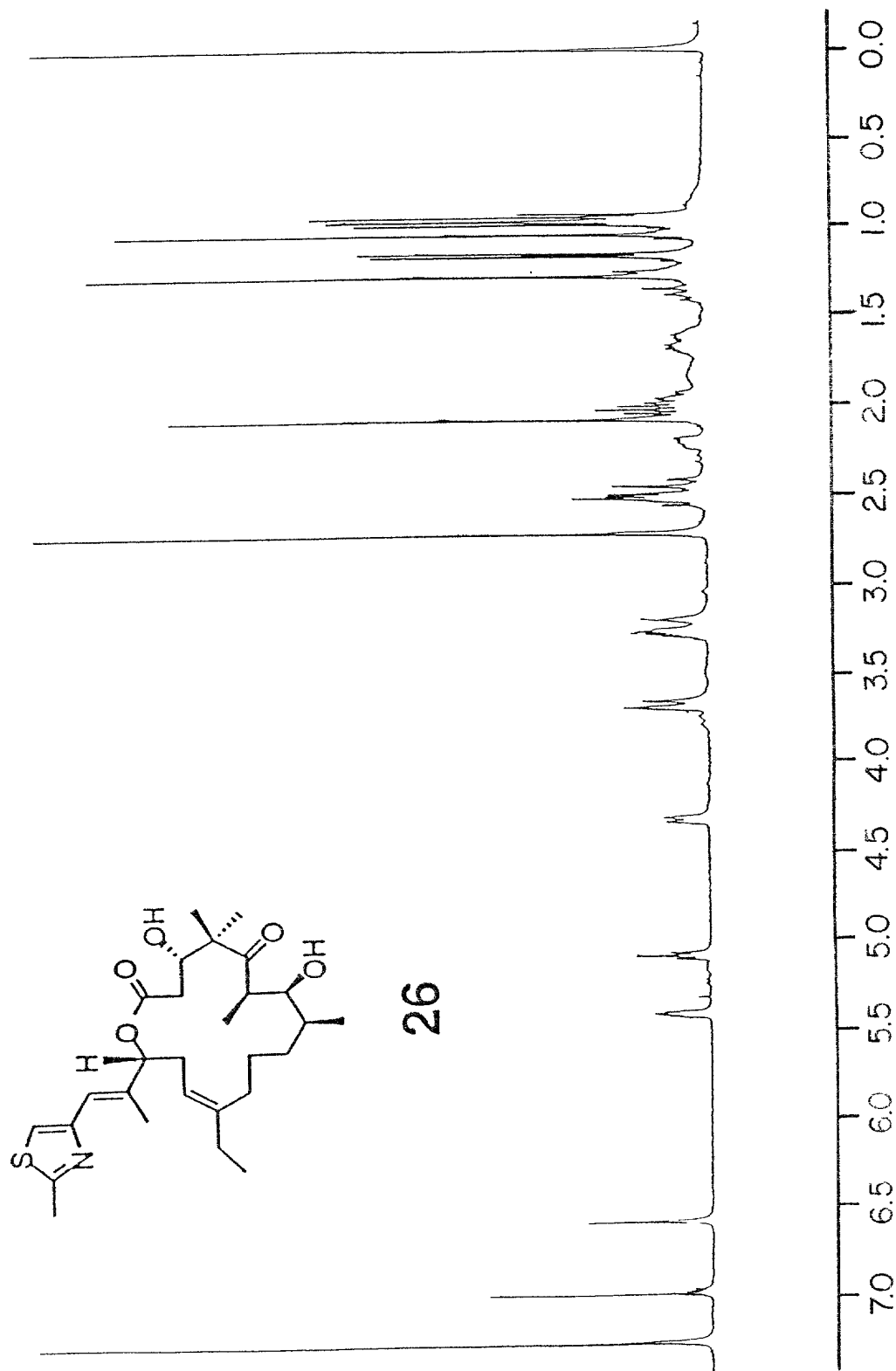


FIG. 37

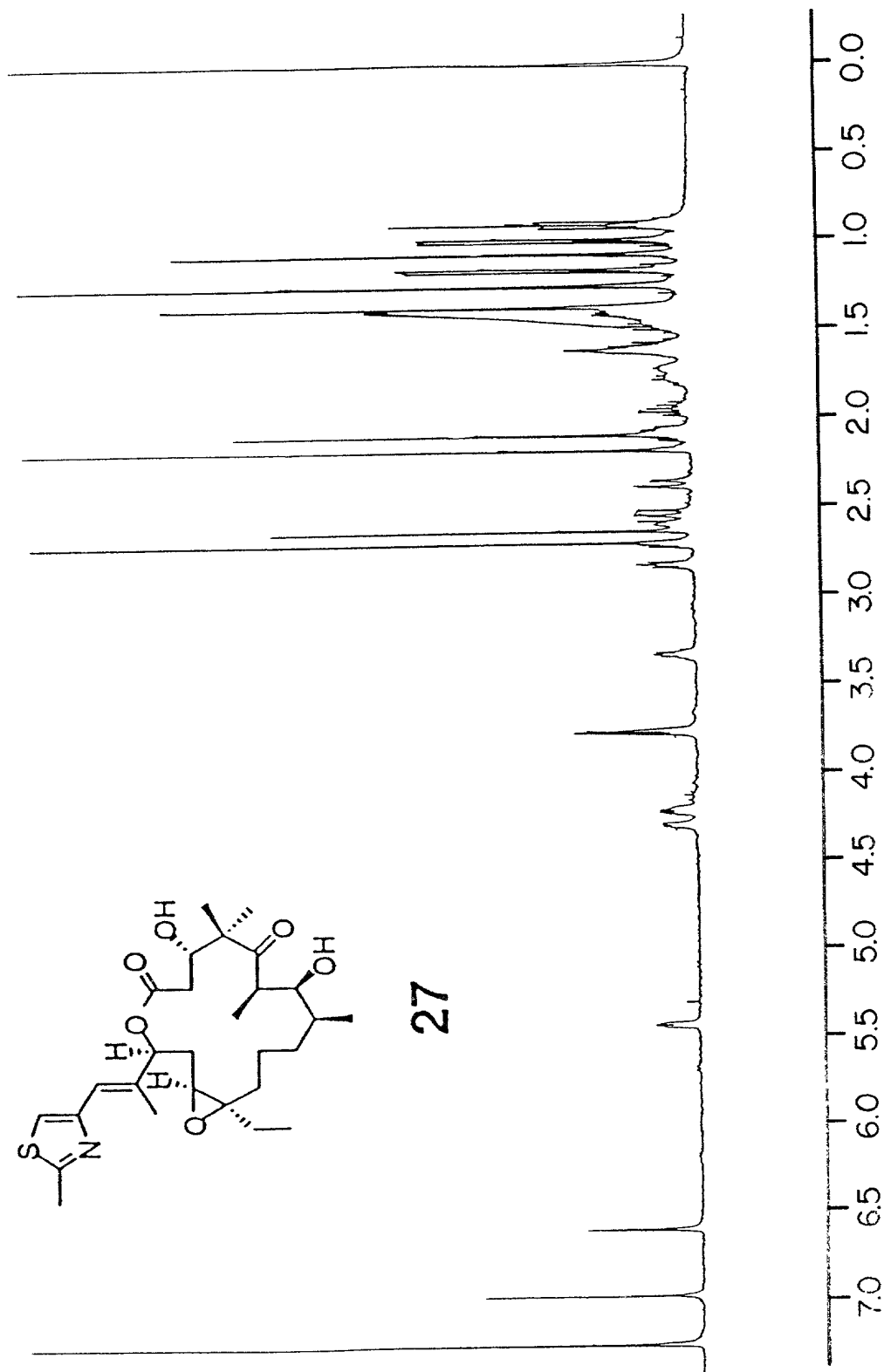


FIG. 38

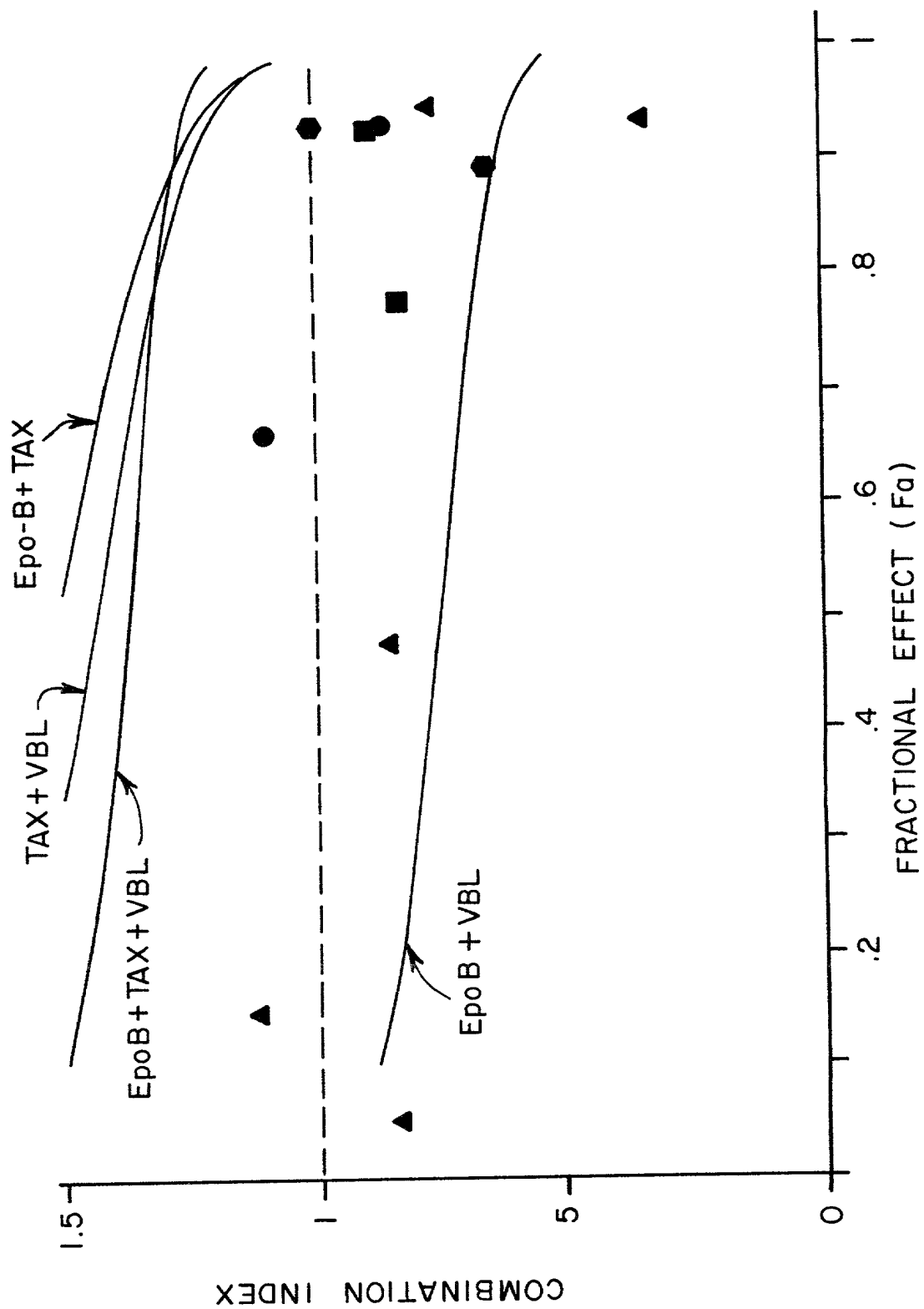
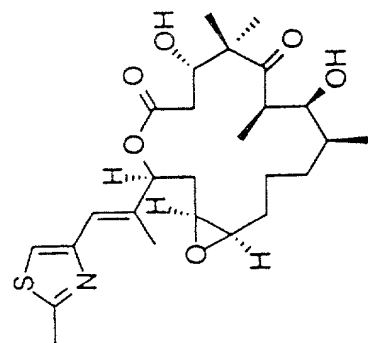
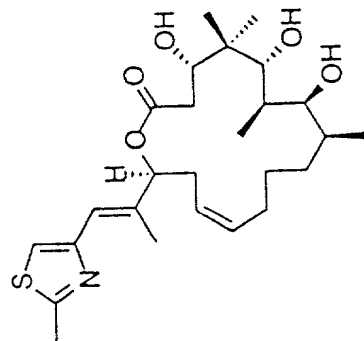


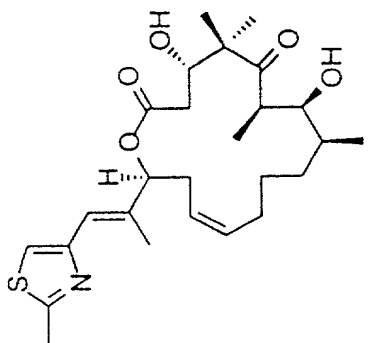
FIG. 39A



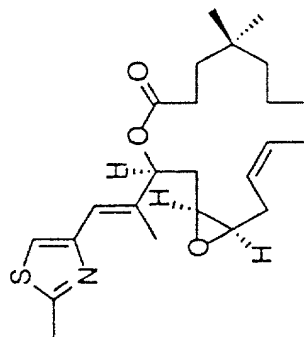
epothilone A
(0.0027)
[0.020]



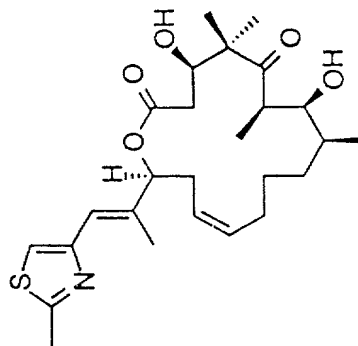
2
(14.23)
[6.28]



desoxyepothilone A
1
(0.022)
[0.012]



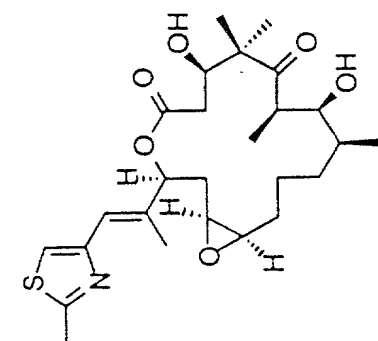
3
(271.1)
[22.4]



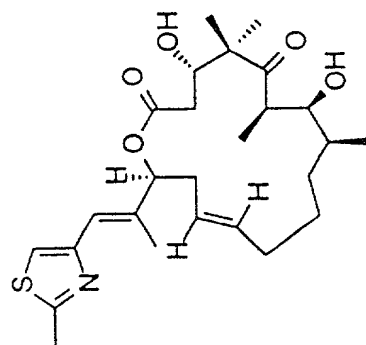
4
(2.12)
[43.0]

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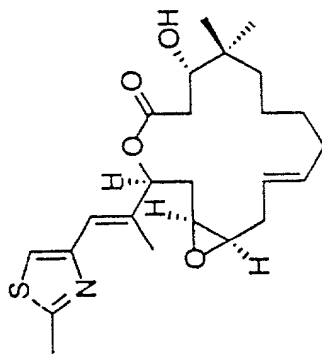
FIG. 39B



5
(>20)
[35.2]

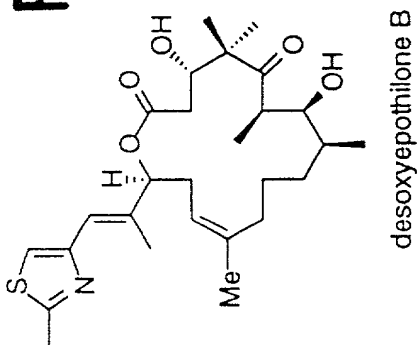


6
(0.052)
[0.035]

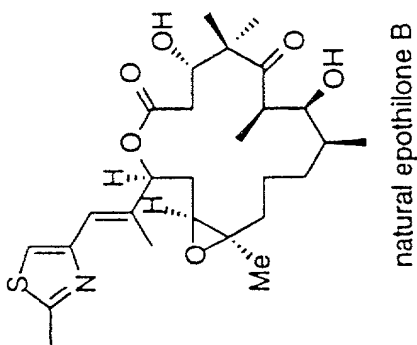


7
(7.36)
[9.82]

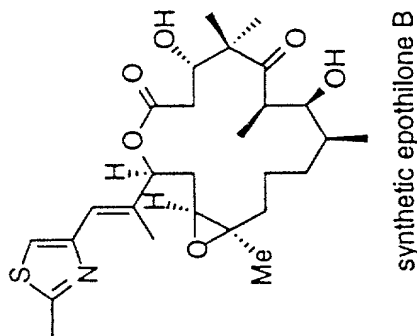
FIG. 40A



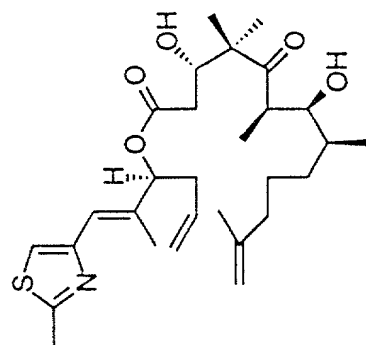
10
(0.0095)
[0.017]



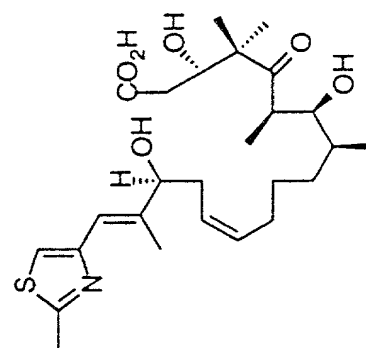
9
(0.00017)
[0.0012]



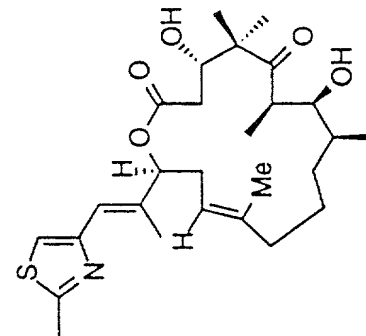
8
(0.00044)
[0.0026]



13
(11.53)
[5.63]



12
(0.79)
[>5]



11
(0.090)
[0.262]

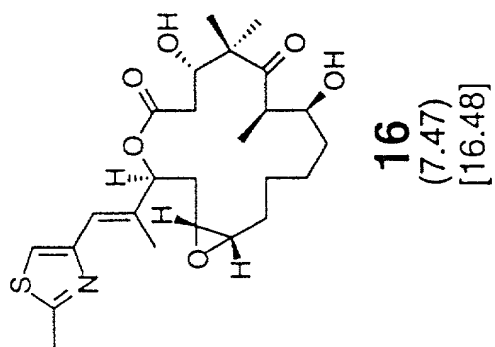
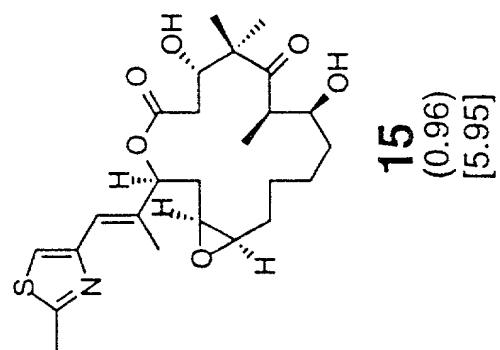
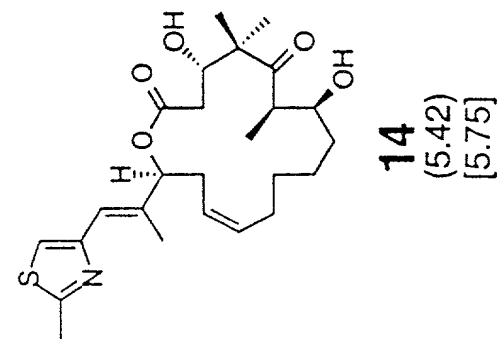


FIG. 40B

FIG. 41A

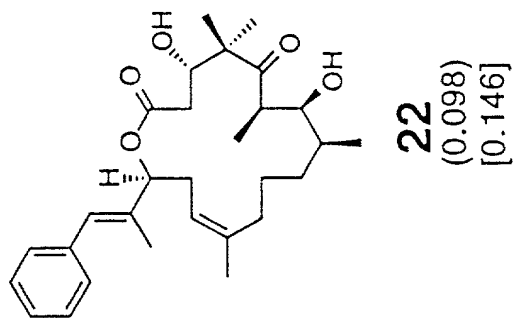
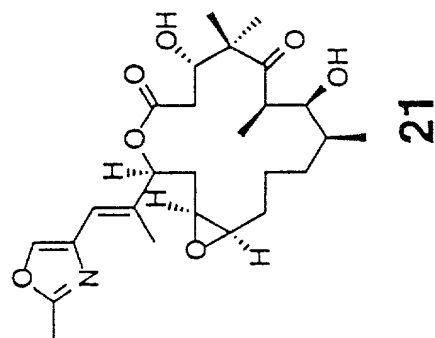
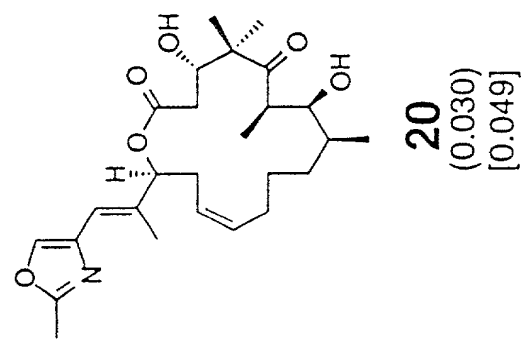
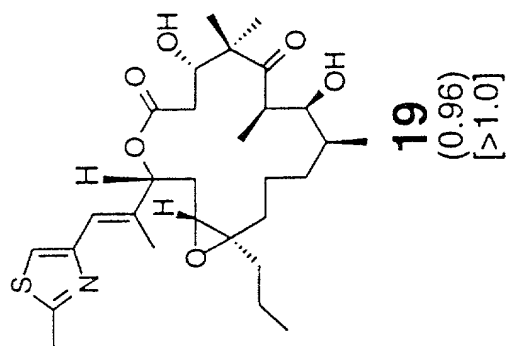
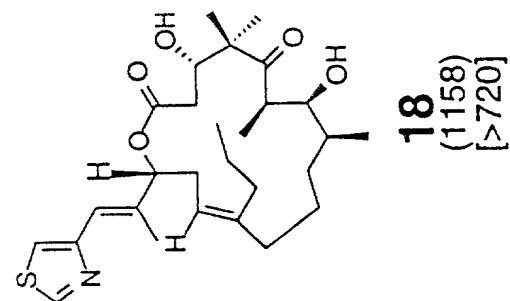
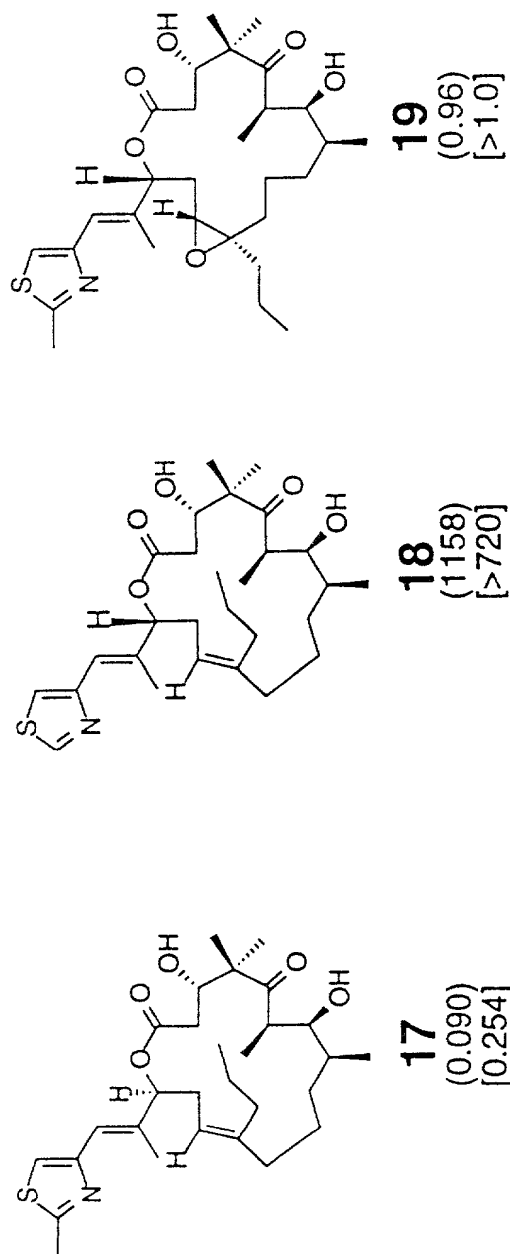
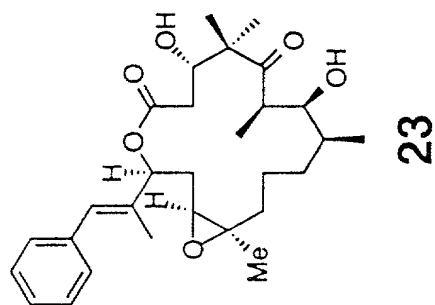
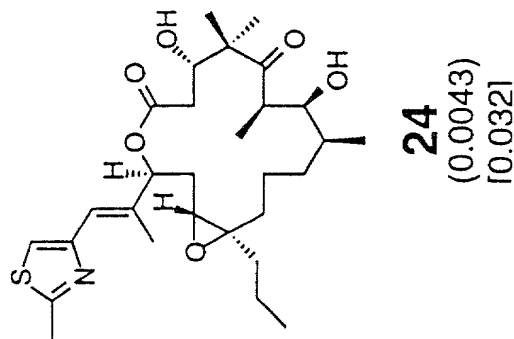


FIG. 41B

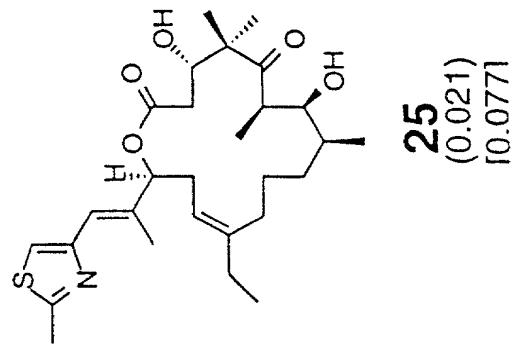


23



24

(0.0043)
[0.032]



25

(0.021)
[0.077]

FIG. 42A

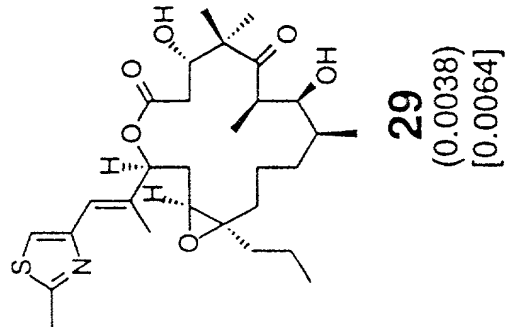
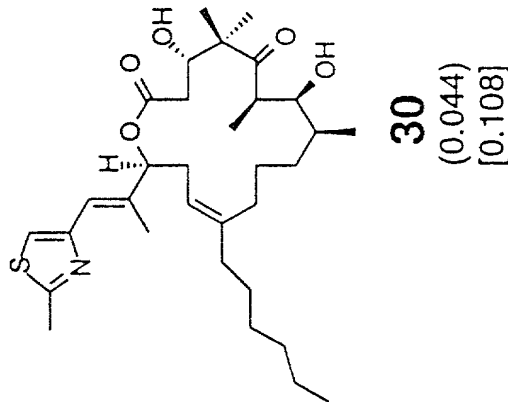
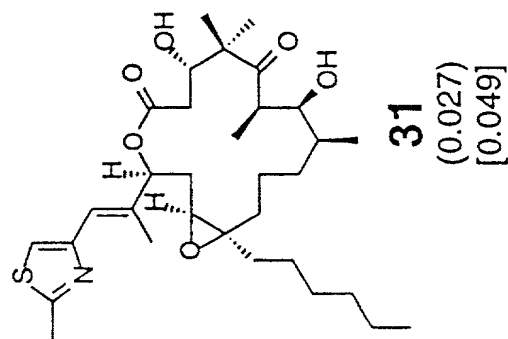
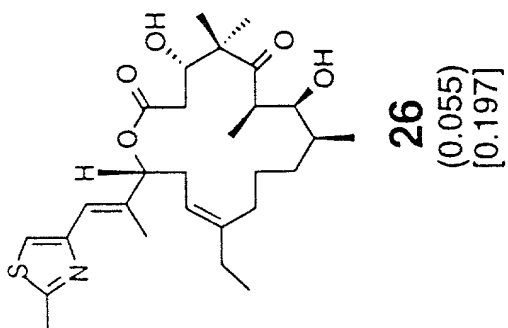
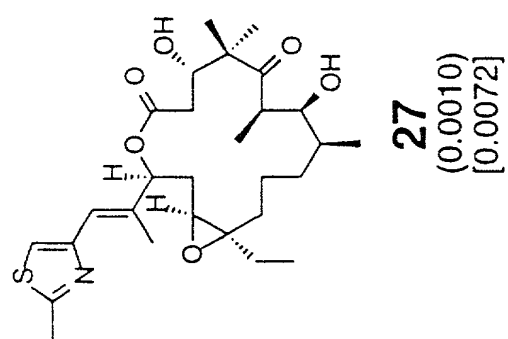
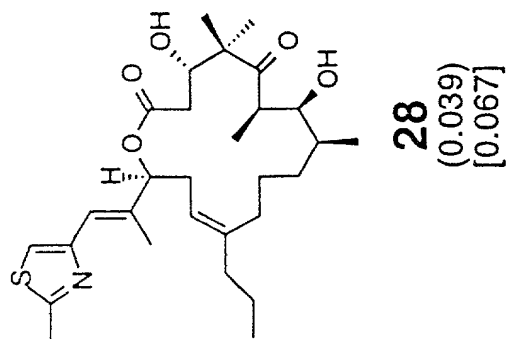


FIG. 42B

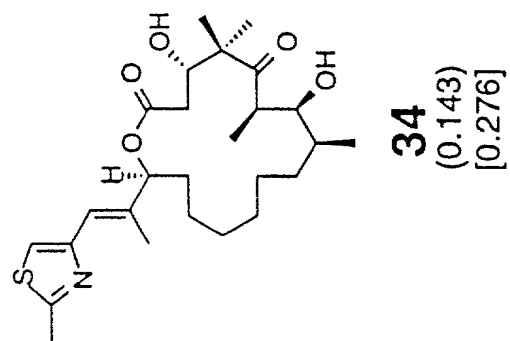
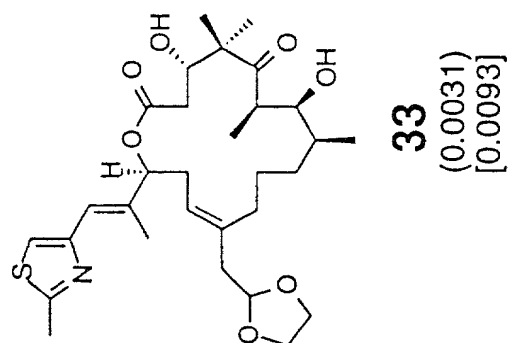
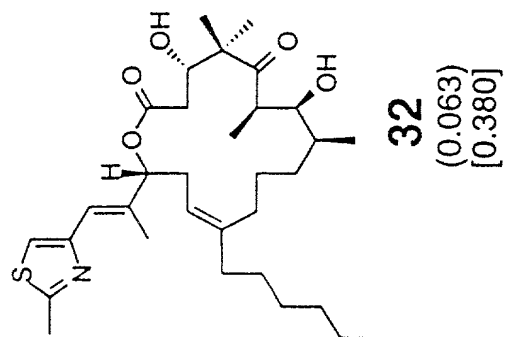


FIG. 42C

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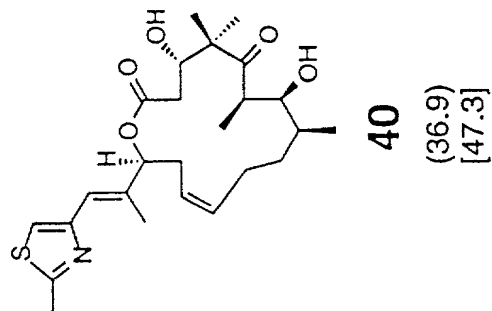
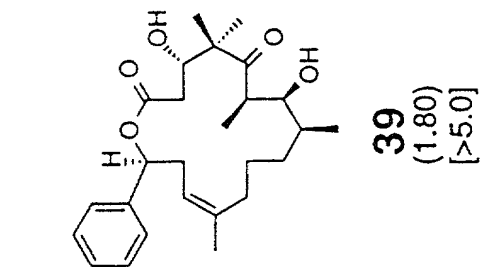
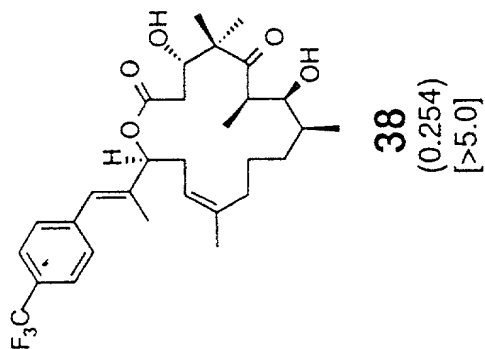
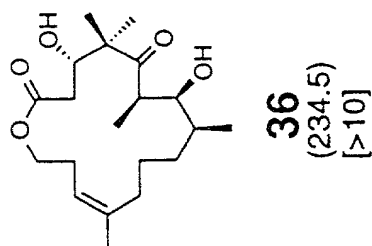
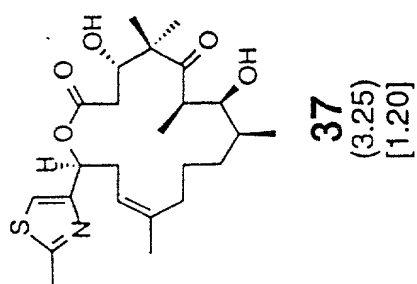
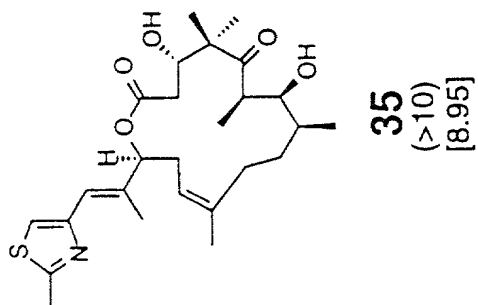
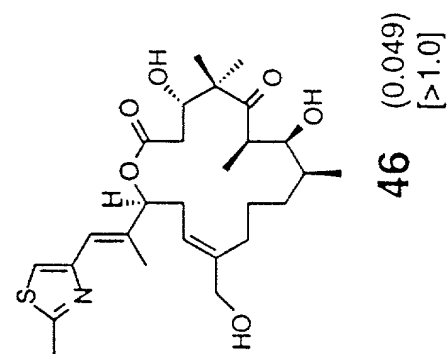
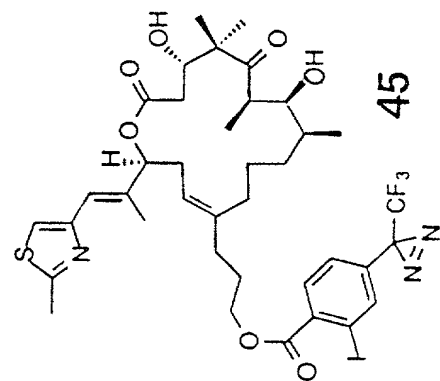
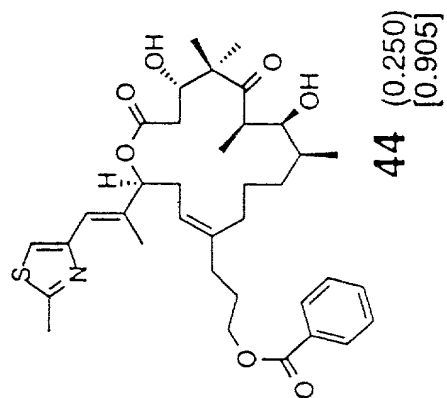
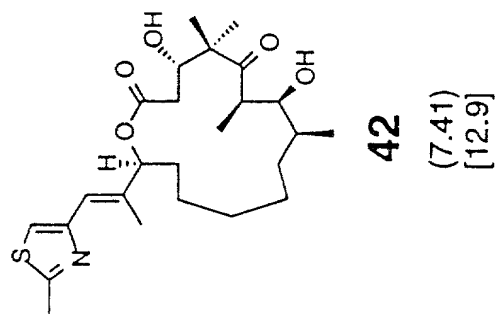
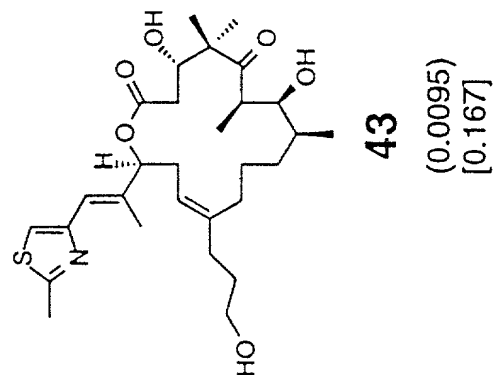
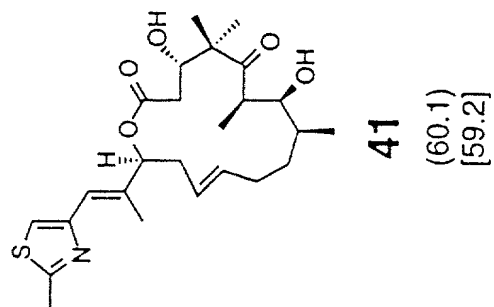
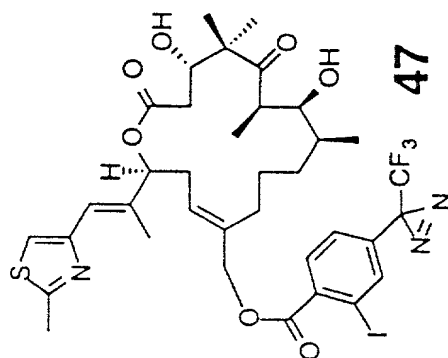
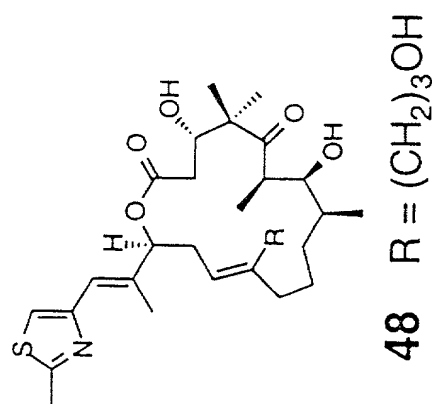
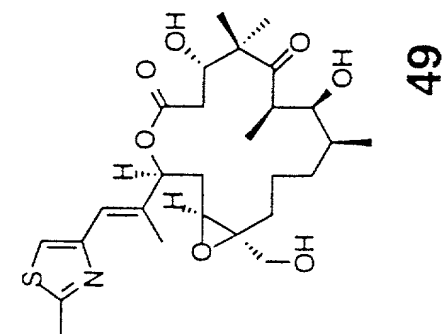


FIG. 42D

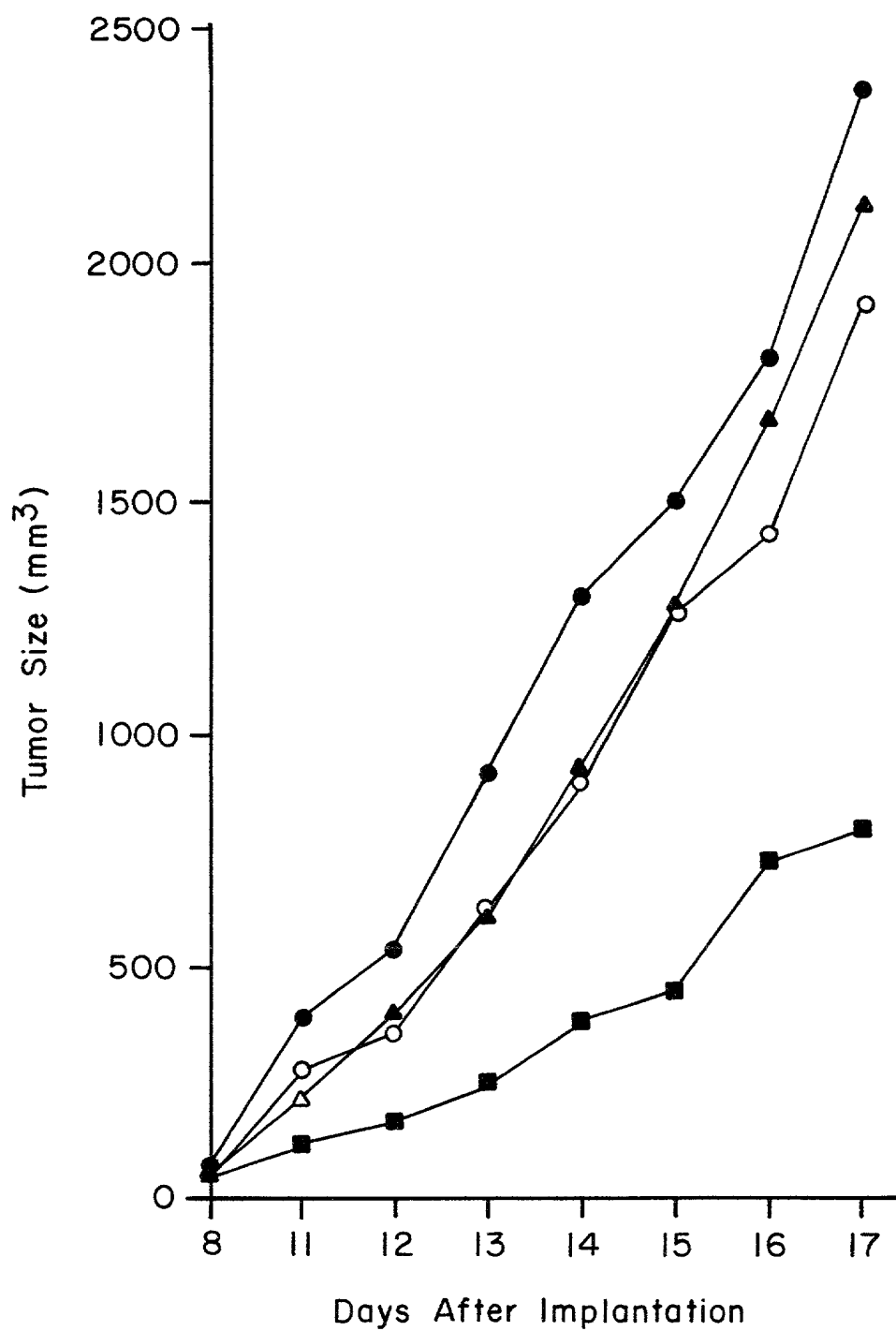


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FIG. 43A



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FIG. 43 B

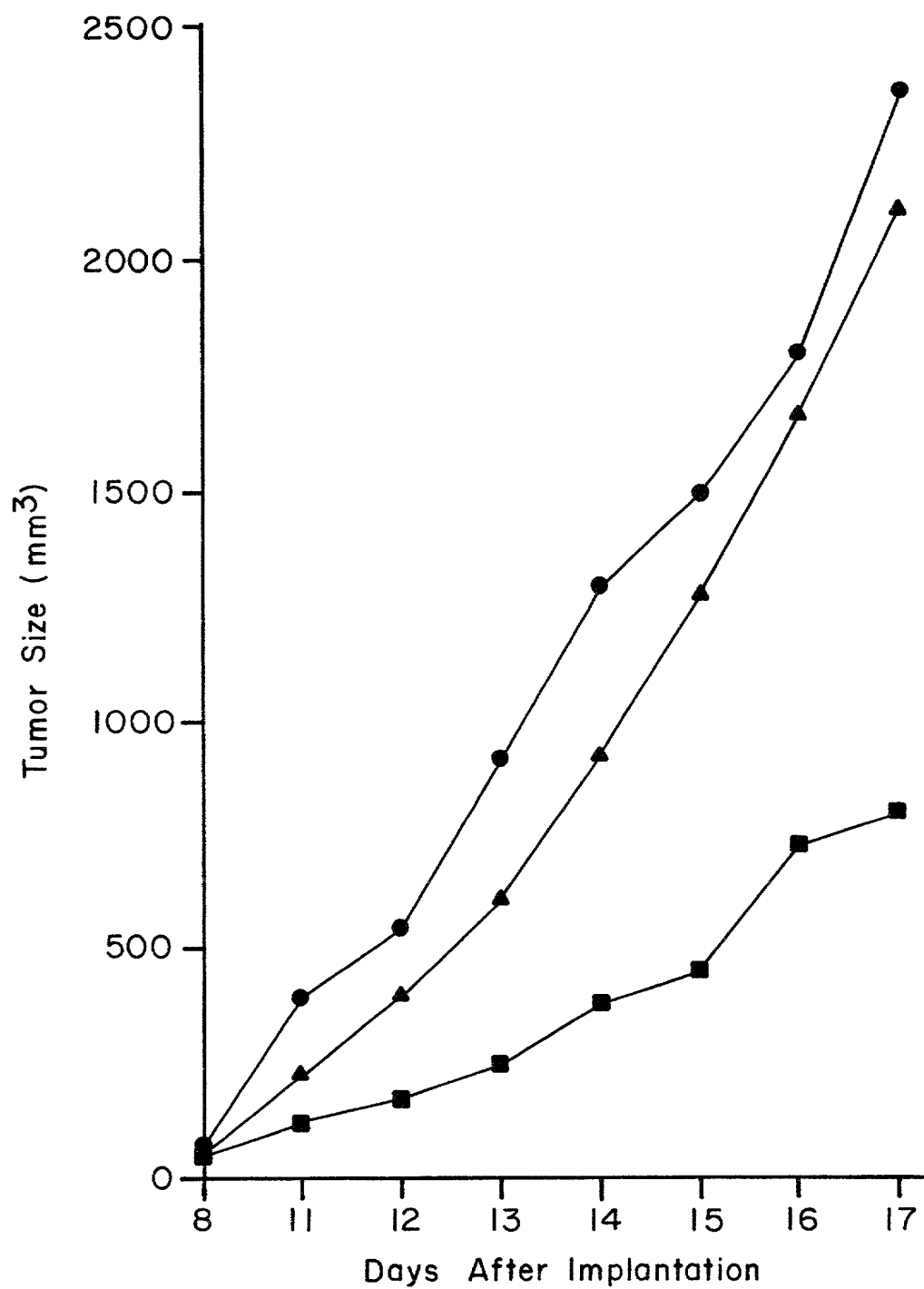
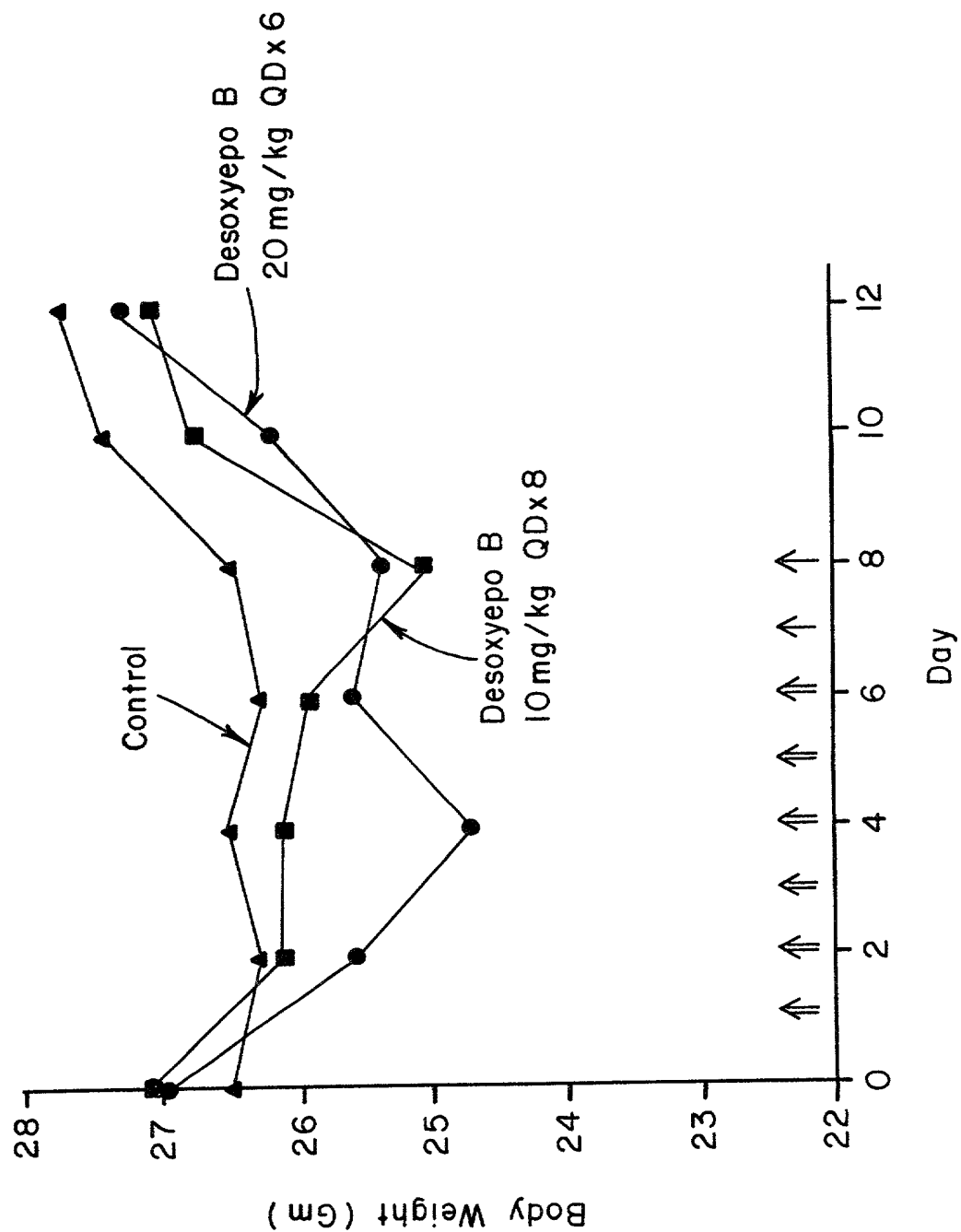
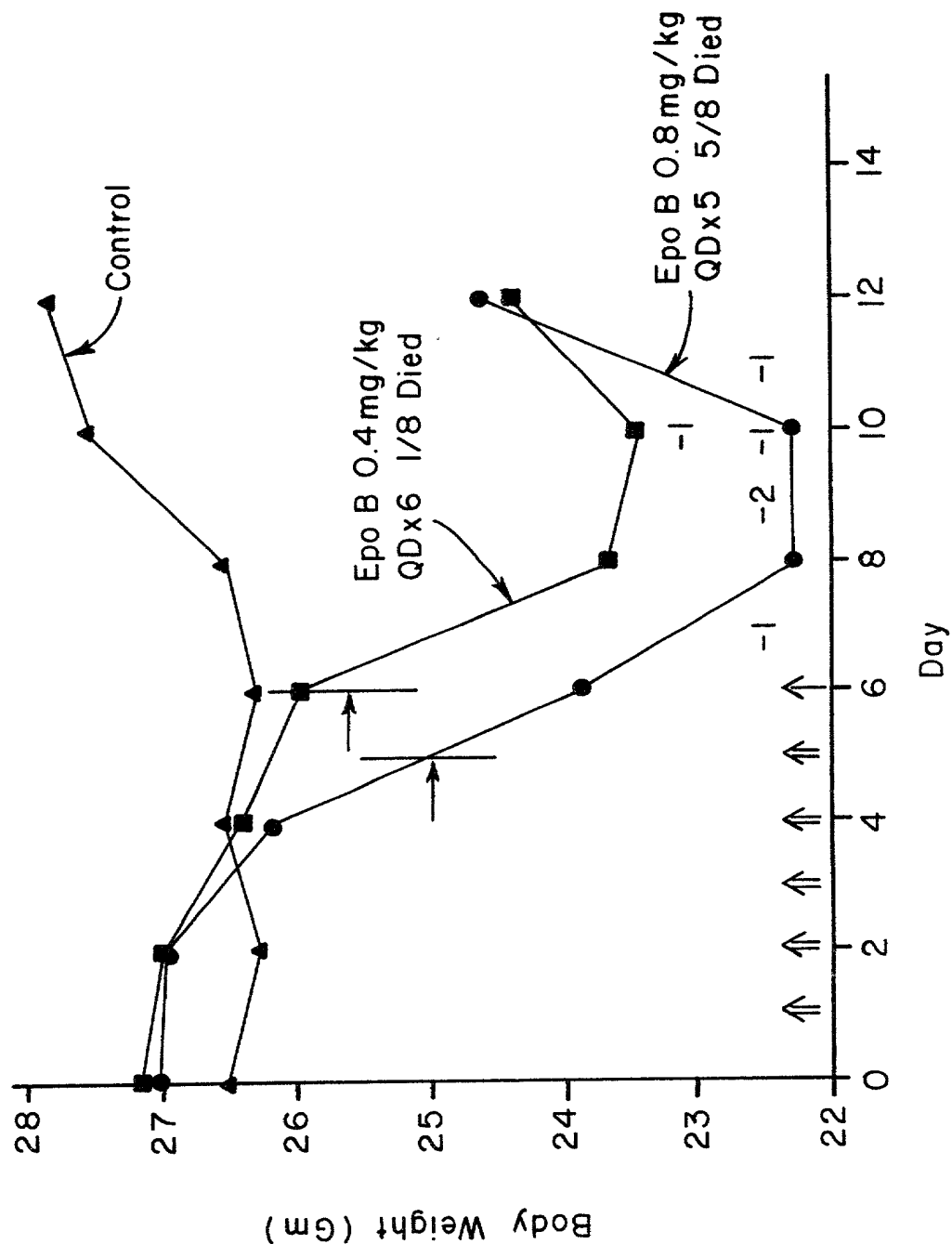


FIG. 44A



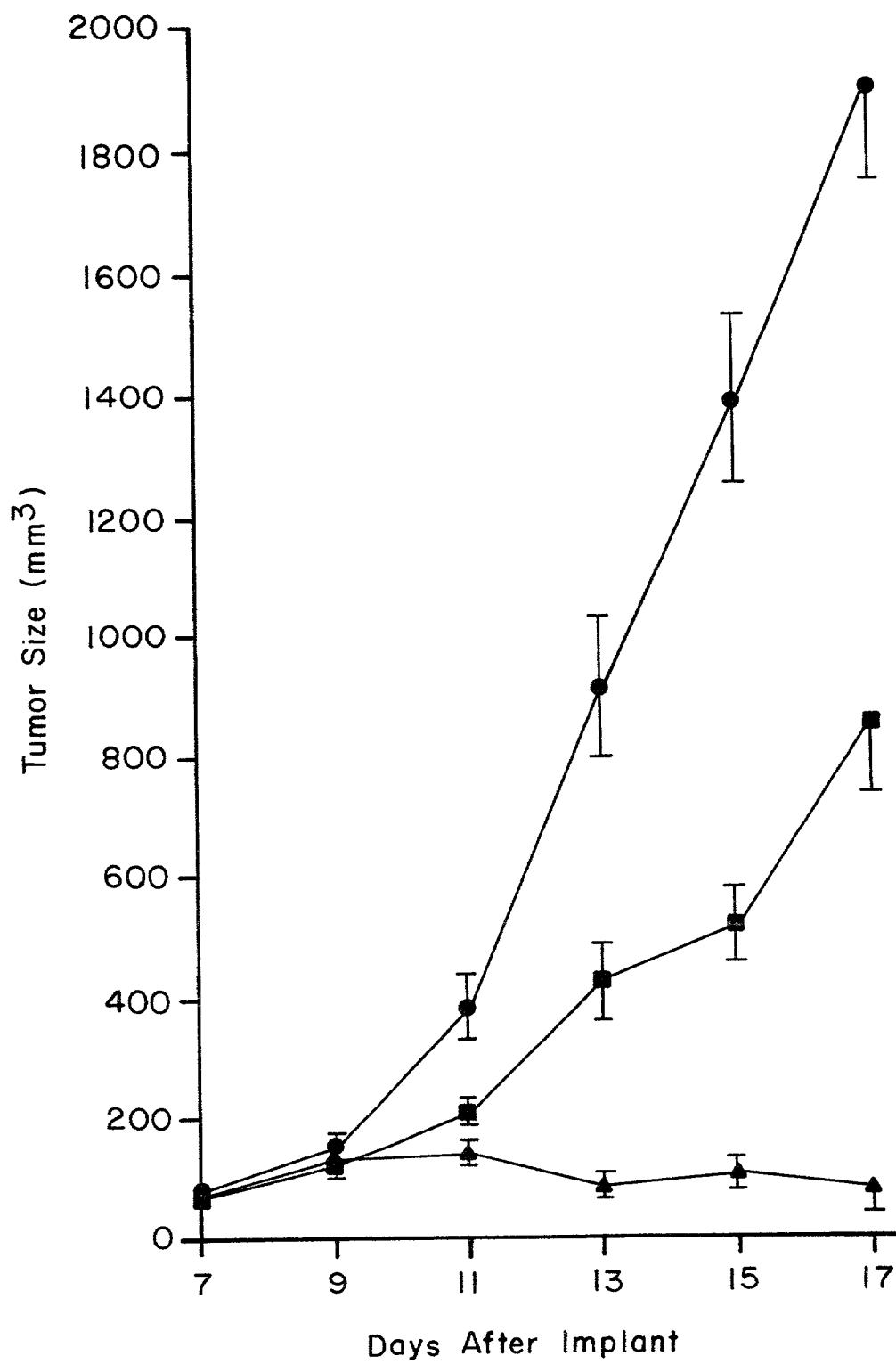
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FIG. 44B



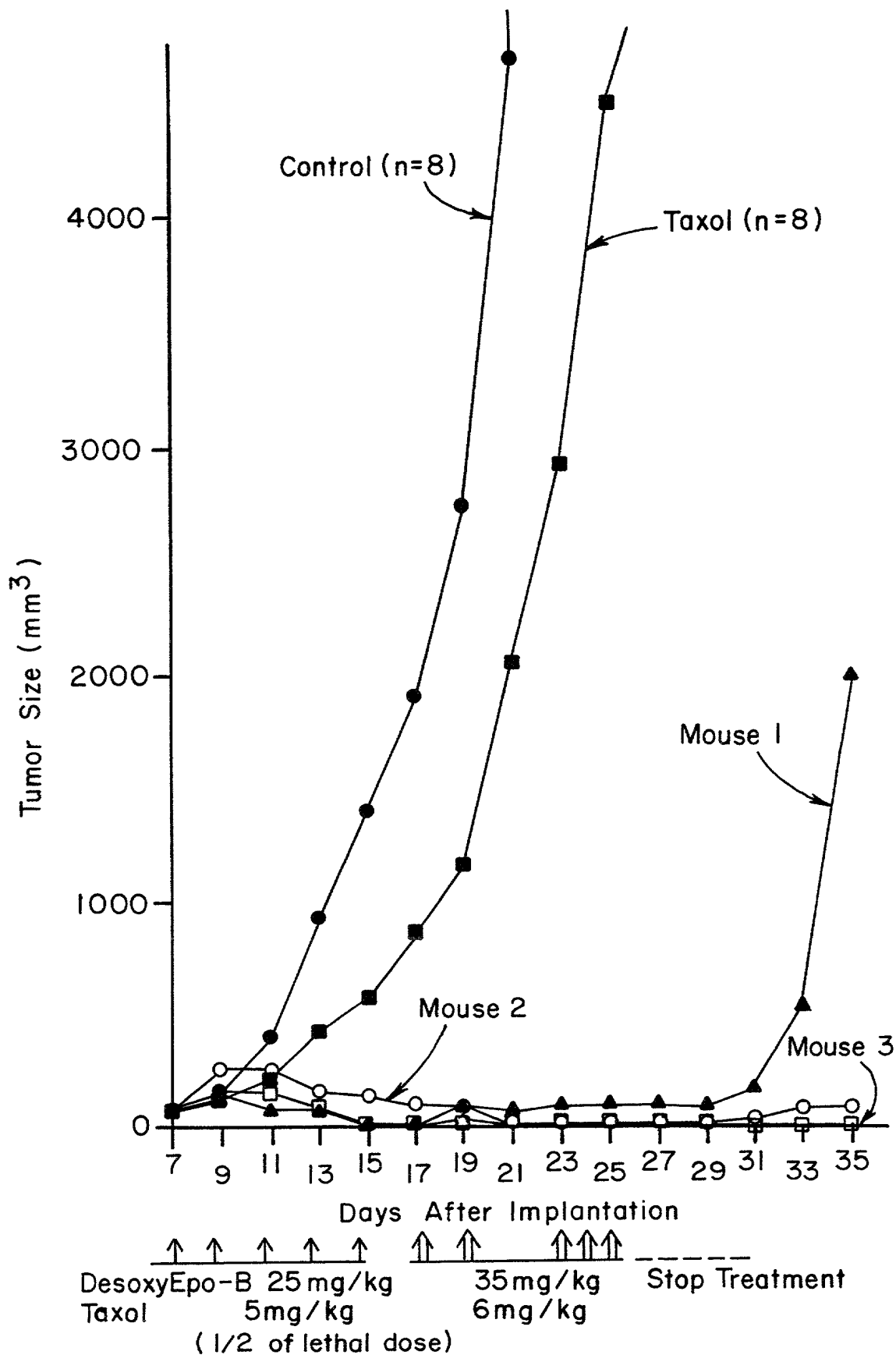
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FIG. 45A



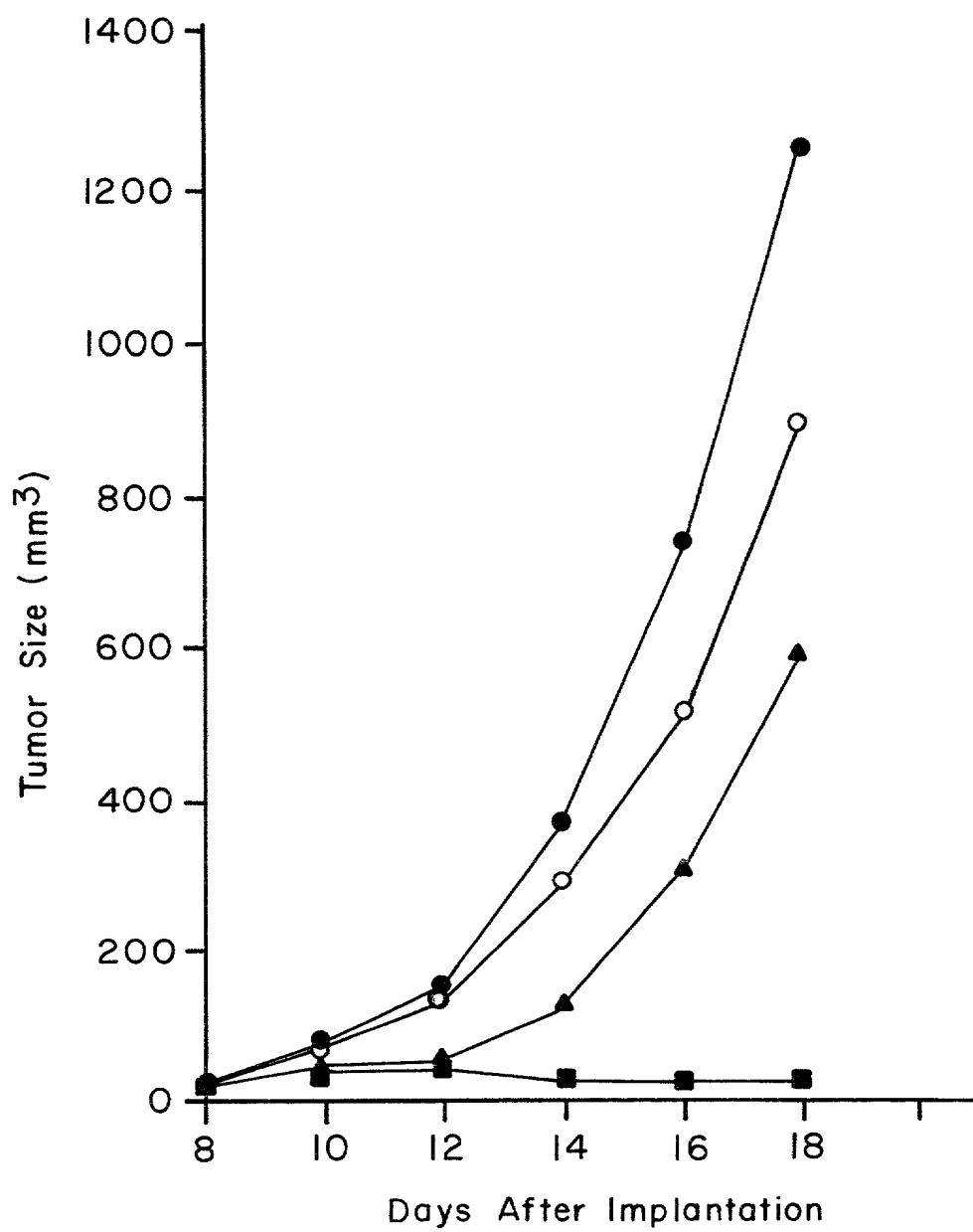
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FIG. 45 B



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FIG. 46



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FIG. 47

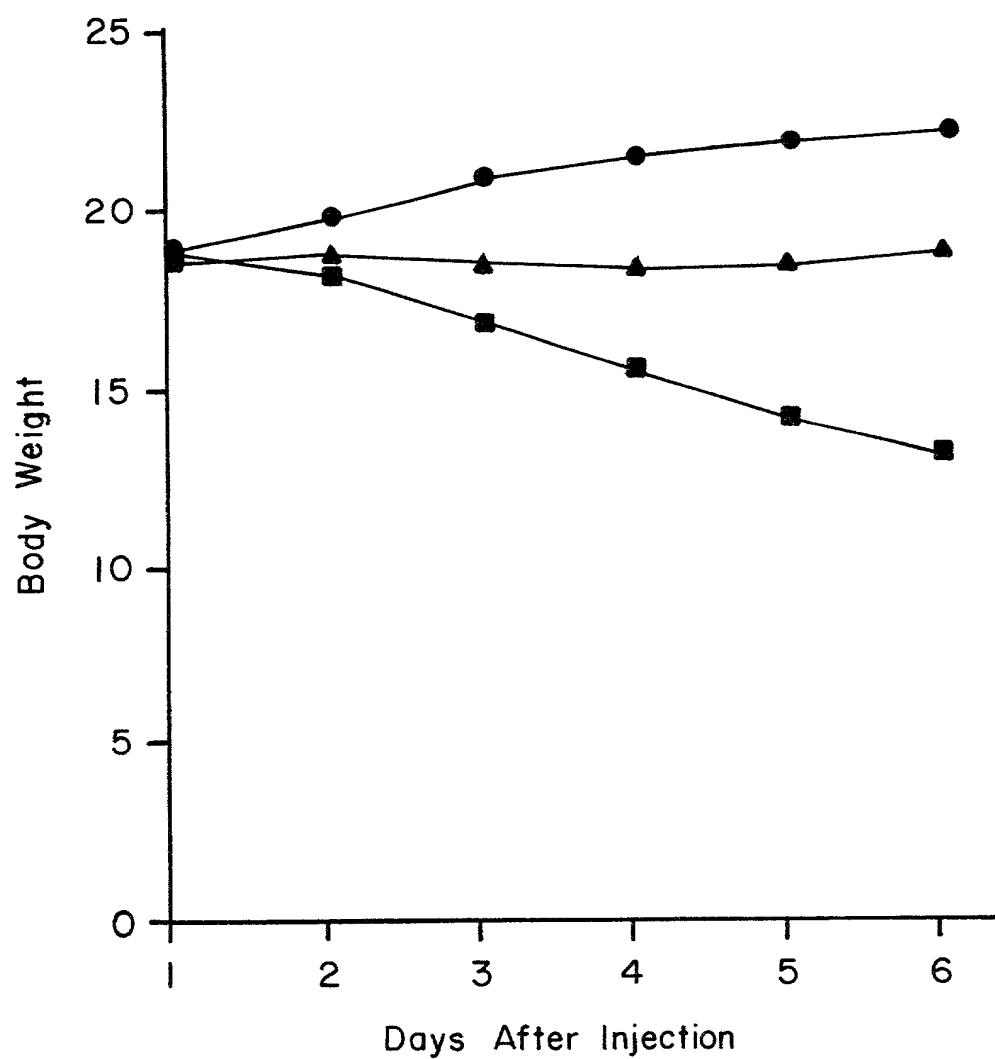


FIG. 48

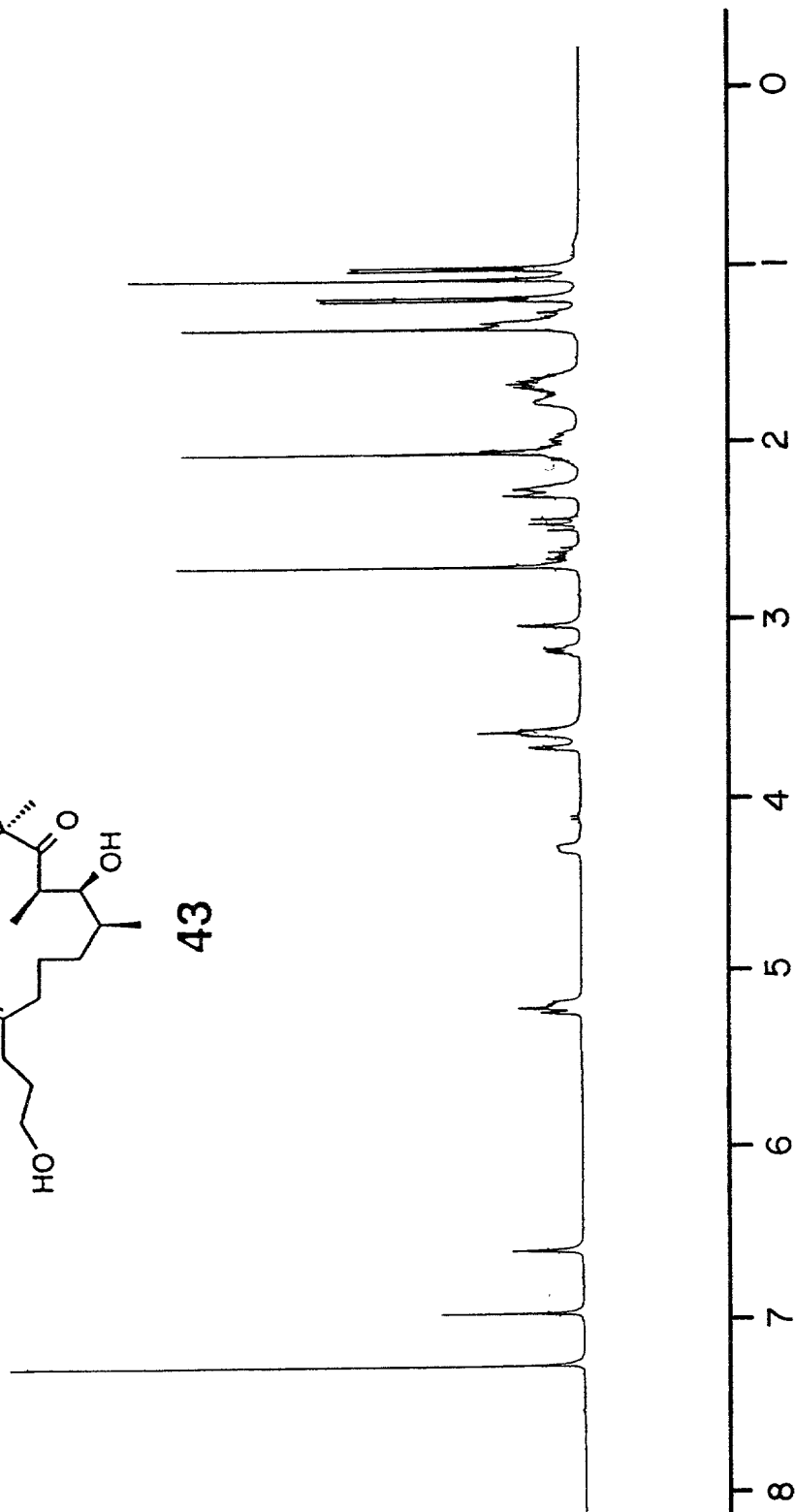
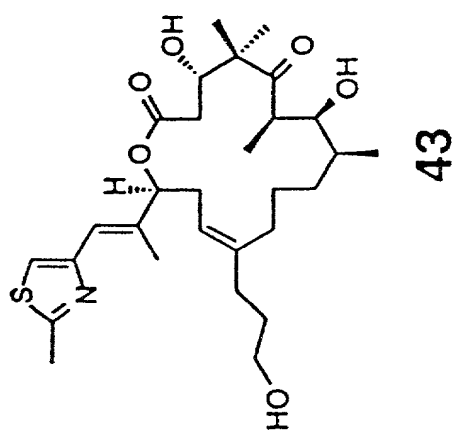
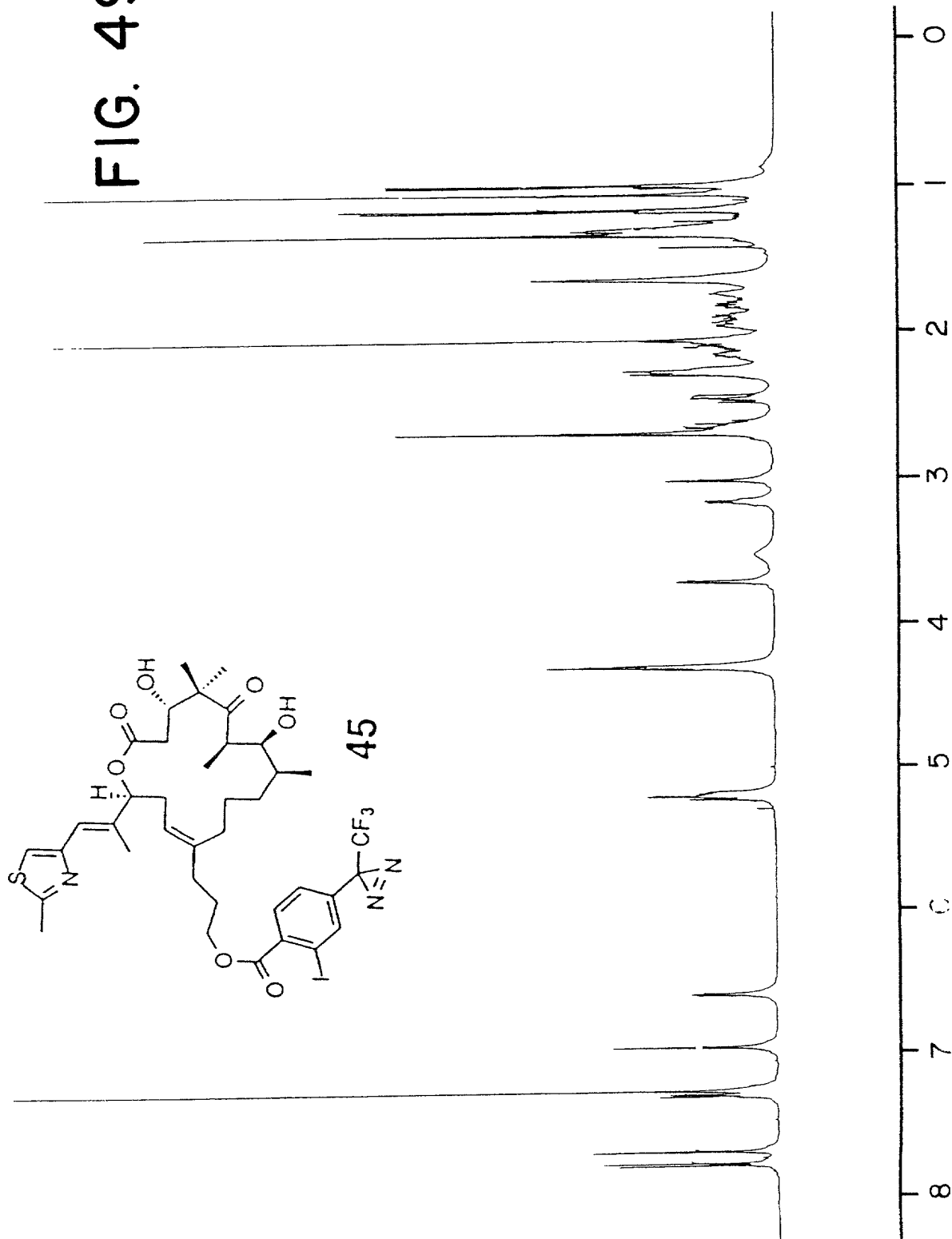


FIG. 49



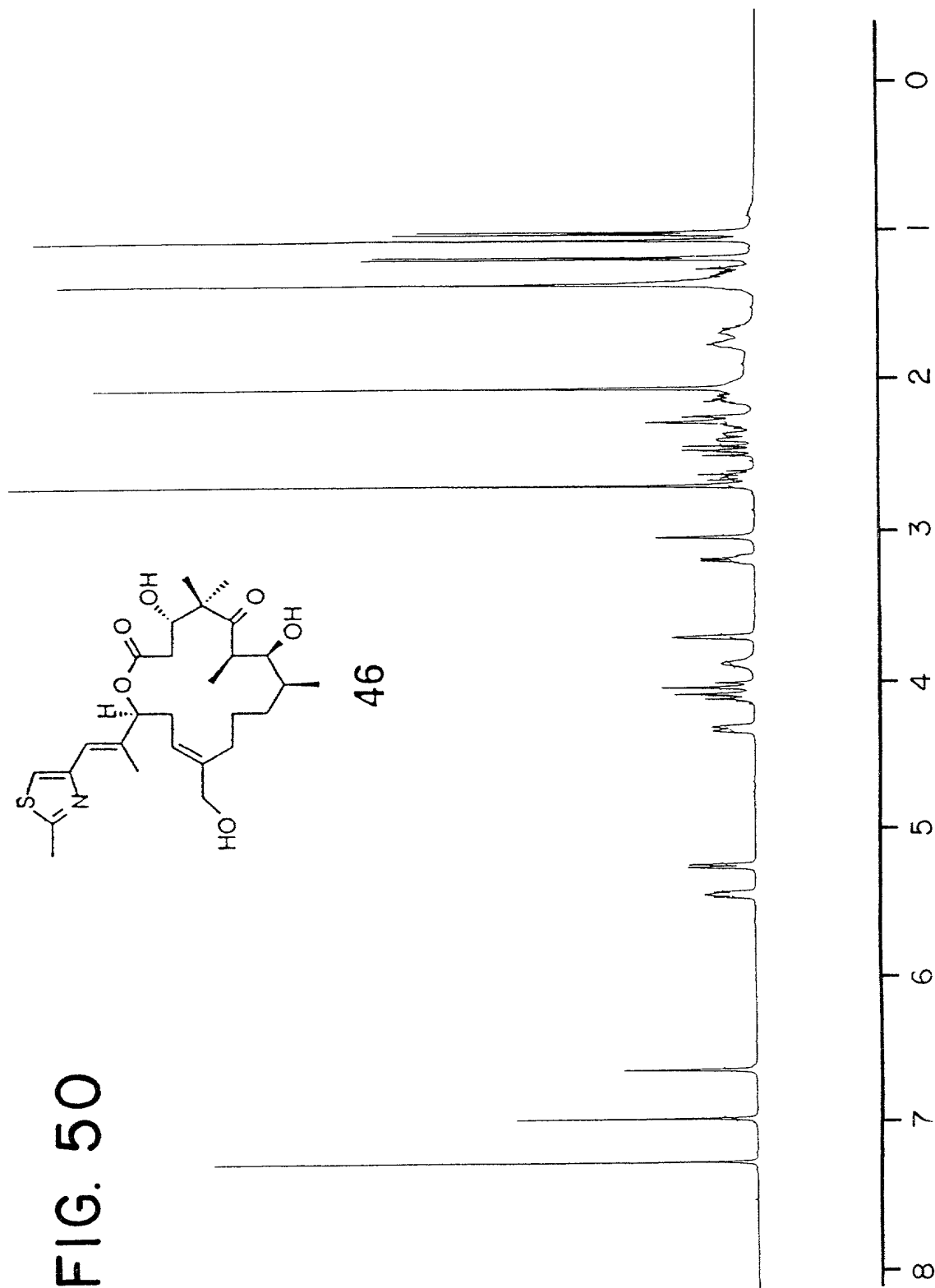


FIG. 51

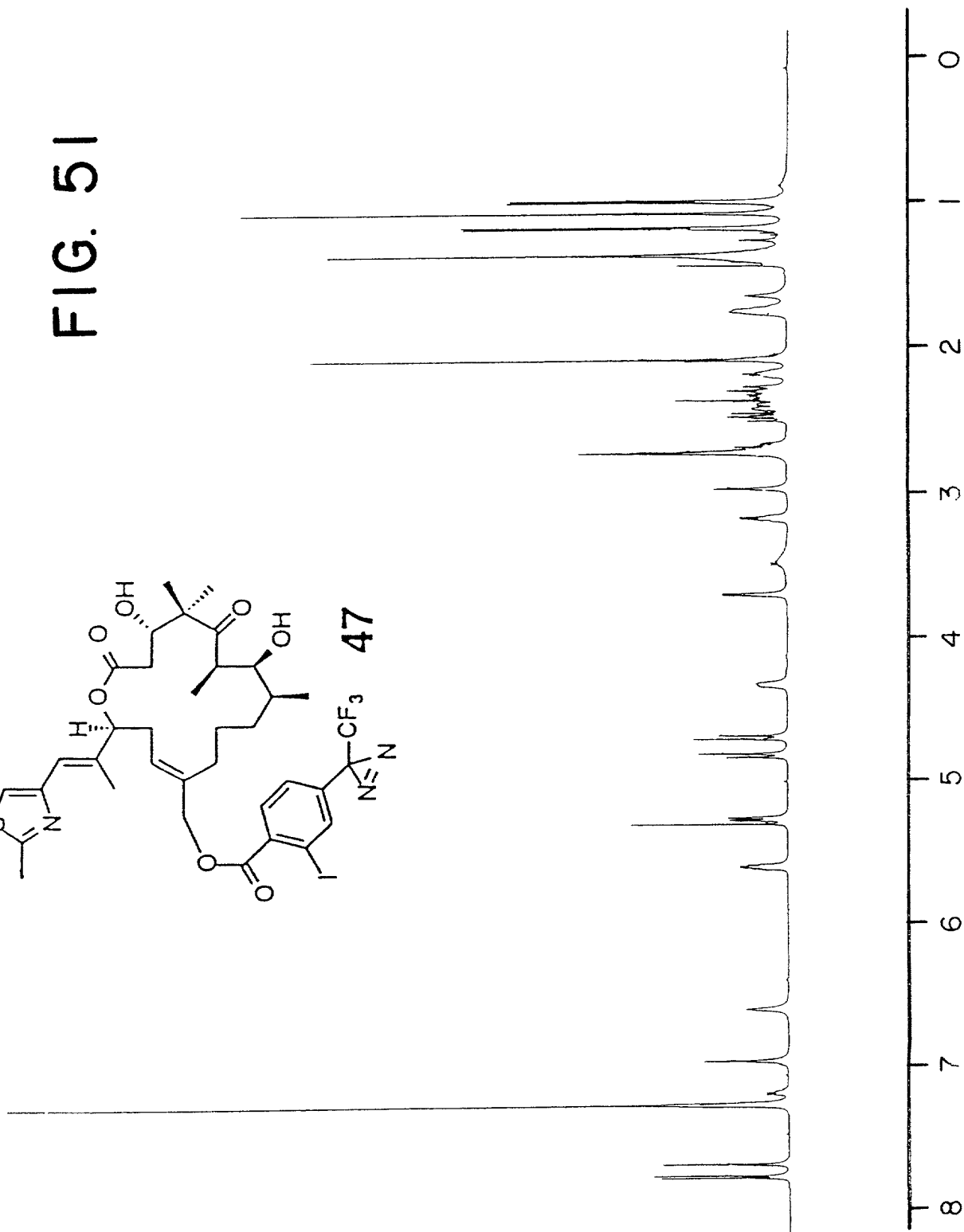
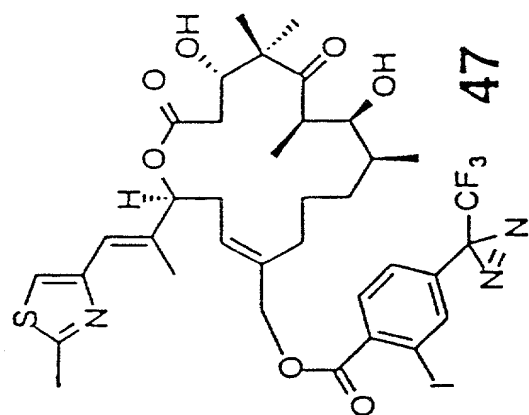
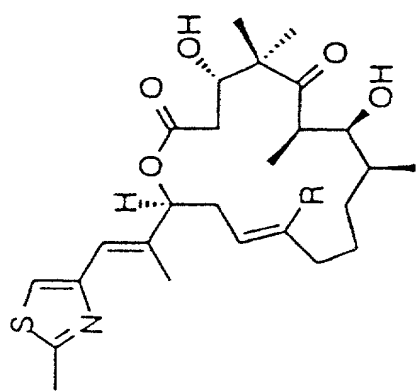


FIG. 52



48 R = (CH₂)₃OH

